Interferon treatment for Japanese patients with favorable-risk metastatic renal cell carcinoma in the era of targeted therapy

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Purpose: Single-agent interferon (IFN) is no longer regarded as a standard option for first-line systemic treatment of metastatic renal cell carcinoma (RCC) in Western countries. However, some patients with favorable-risk RCC may still achieve complete and long-lasting remission in response to IFN treatment. The present study compared favorable-risk Japanese patients with metastatic RCC Japanese patients who had been treated with IFN or tyrosine kinase inhibitor (TKI) therapy as a first-line systemic therapy.

Materials and Methods: From 1995 to 2014, a total of 48 patients with favorable risk as defined by the Memorial Sloan Kettering Cancer Center criteria who did not receive adjuvant systemic therapy were retrospectively enrolled in this study. We assessed the tumor response rate, progression-free survival (PFS), and overall survival (OS).

Results: The objective response rate for first-line therapy was 29% in the IFN group and 47% in the TKI group, but this difference did not reach the level of statistical significance. Median OS for IFN and TKI was 71 and 47 months, respectively (p=0.014). Median first-line PFS for IFN and TKI was 20 and 16 months, respectively (no significant difference). First-line IFN therapy did not prove inferior to TKI therapy in terms of OS according to metastatic sites.

Conclusions: IFN is associated with a survival benefit in Japanese patients with favorable-risk metastatic RCC in the era of targeted therapy. Further prospective study is needed.

Keywords: Interferons; Protein-tyrosine kinases; Renal cell carcinoma

INTRODUCTION

There are 209,000 cases of and 102,000 deaths due to renal cell carcinoma (RCC) per year worldwide. The incidence of all stages of RCC has increased over the past several years [1]. RCC had been treated with cytokines with a modest response rate and some survival benefit [2]. Since 2005, the U.S. Food and Drug Administration and European Medicines Agency have approved novel agents targeting the vascular endothelial growth factor pathways for patients with metastatic RCC (mRCC) on the basis of the results of large randomized clinical trials. Single-agent interferon (IFN) is no longer regarded as a standard option for first-line systemic treatment of mRCC in Western countries [1].

In a large cohort in a retrospective Japanese study, the

median survival time was approximately twice as long as that in previous studies from North America and Europe in the cytokine era. One of the reasons for the difference was considered to be related to varying individual sensitivities to cytokine treatments. Racial differences might also affect biological characteristics of the tumors, leading to differences in frequencies of metastatic lesions and pathological features [3].

Previous reports demonstrated positive response rates of 10% to 20% in response to cytokine treatments. However, some patients with favorable-risk disease achieved a complete and long-lasting remission [4,5]. Recent studies suggest that STAT3 polymorphism predicts a favorable response and survival benefit of IFN-alpha in Japanese patients with mRCC [6].

Thus, cytokine treatments may be useful for some Japanese patients with mRCC, even in the era of targeted therapy. The present study investigated outcomes in Japanese patients with favorable-risk mRCC according to the Memorial Sloan Kettering Cancer Center (MSKCC) criteria who had been treated with IFN or tyrosine kinase inhibitor (TKI) therapy as a first-line systemic therapy.

MATERIALS AND METHODS

A total of 48 Japanese mRCC patients with favorable-risk disease as defined by the MSKCC criteria who had been treated with immunotherapy or TKI therapy at Chiba University Graduate School of Medicine Hospital (CU) or Chiba Cancer Center (CCC), Japan, from 1995 to 2014 were retrospectively enrolled in this study. Ten patients were treated with TKI therapy as a first-line therapy at CCC; the others were treated at CU. Patients who had received adjuvant systemic therapy were excluded. The MSKCC criteria included Karnofsky performance status <80%, elevated lactate dehydrogenase, low hemoglobin, elevated serum corrected calcium, and time from diagnosis to starting systemic therapy <1 year. Favorable-risk patients have 0 risk factors [7].

Data regarding clinical characteristics, including age, gender, clinical stage, histology of the primary tumor, metastasectomy, radiation, and radiofrequency ablation (RFA), were collected from 48 patients. If necessary, we performed metastasectomy, RFA, and radiation before and during systemic treatment. In principle, we performed metastasectomy when the patient would be a surgical complete response (CR). Because systemic treatment response in liver metastasis was low in many cases, we tried to perform RFA for liver metastasis if possible.

First-line systemic IFN therapy included IFN-alpha and IFN-gamma in 29 and 2 cases, respectively. First-line systemic TKI therapy included sorafenib, sunitinib, and axitinib in five, eight, and four cases, respectively. First-line progression-free survival (PFS), overall survival (OS), and first-line response rate were evaluated in all 48 patients. Second-line PFS was evaluated in 24 patients.

After sorafenib was approved for clinical use in 2008, we began to examine its clinical application for other potential molecular targets. We assessed the tumor response according to the RECIST (response evaluation criteria in solid tumors). PFS and OS were calculated from the date of initial systemic therapy. Statistical analysis was performed by using the Student t-test, chi-square test, or Mann-Whitney U test, and survival curves (PFS and OS) were created by using the Kaplan-Meier method with the log-rank test. Values of $p<0.05$ were considered to represent statistical significance. SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

RESULTS

Comparisons of the clinical and pathological features of all 48 patients according to first-line therapy are summarized in Table 1. The mean age at diagnosis was 60 years in the IFN group and 58 years in the TKI group (no significant difference). There was no significant difference between the two groups in distribution of gender. Before 2008, all patients were treated by immunotherapy. Since 2008, 10 patients were treated with IFN and 17 patients were treated with TKI as a first-line therapy. All 48 patients enrolled in this study underwent nephrectomy. The initial clinical stage was 1 in 13 cases (42%), 2 in 7 cases (23%), 3 in 10 cases (32%), and 4 in 1 case (3%) in the IFN group. The initial clinical stage was 1 in six cases (35%), 2 in three cases (18%), 3 in four cases (24%), and 4 in four cases (24%) in the TKI group. Stage 4 was much more frequent in the TKI group than in the IFN group (p=0.0276). Histology was the clear-cell type in 26 cases (84%), sarcomatoid in 2 cases (6%), collecting duct in 2 cases (6%), and chromophobe in 1 case (3%) in the IFN group. The histology of all TKI cases was the clear-cell type.

Metastasectomy from any organ was performed in 12 patients (39%) in the IFN group and in 8 patients (48%) in the TKI group. Radiation of any site was performed in three (10%) and one (6%) patient, respectively, and RFA to any organ was performed in two (6%) and two (12%) cases, respectively. Duration from nephrectomy to systemic therapy was 34.1 months in the IFN group and 47.3

**Table 1.** Comparison of patient characteristics between the two groups

Characteristic	Treatment strategy		p-value
	IFN (n=31)	TKI (n=17)	
Age (y)	60 (40–74)	58 (41–76)	0.846
Systemic therapy start			<0.001
Before 2008	21 (68)	0 (0)	
Since 2008	10 (32)	17 (100)	
Gender			0.839
Male	21 (68)	12 (71)	
Female	10 (32)	5 (29)	
Nephrectomy	31 (100)	17 (100)	1.000
Stage			
1	13 (42)	6 (35)	
2	7 (23)	3 (18)	
3	10 (32)	4 (24)	
4	1 (3)	4 (24)	0.028[a]
Histology			
Clear	26 (84)	17 (100)	0.080[b]
Sarcomatoid	2 (6)	0 (0)	
Collecting duct	2 (6)	0 (0)	
Chromophobe	1 (4)	0 (0)	
Metastatectomy	12 (39)	8 (48)	0.575
Radiation	3 (10)	1 (6)	0.649
RFA	2 (6)	2 (12)	0.524
Duration from nephrectomy (mo)	34.1 (12–184)	47.3 (12–133)	0.281

Values are presented as median (range) or number (%).
IFN, interferon; TKI, tyrosine kinase inhibitor; RFA, radiofrequency ablation.
[a]:Stage 4 vs. the others. [b]:Clear vs. the others.

months in the TKI group. Initial stage seemed to affect the duration of starting systemic therapy from nephrectomy. There was no significant difference in the duration from nephrectomy to systemic therapy when comparing the two groups.

In the IFN group, responses included CR in 3 cases (10%), partial response (PR) in 6 cases (19%), stable disease (SD) in 18 cases (58%), and progressive disease (PD) in 4 cases (13%). In the TKI group, responses included CR in one case (6%), PR in seven cases (41%), SD in nine cases (53%), and PD in 0 cases (Fig. 1). The CR rate was higher in the IFN group than in the TKI group, and the objective response rate (ORR) and clinical benefit were higher in the TKI group than in the IFN group, but these differences did not reach the level of statistical significance (p=0.649, p=0.212 and p=0.122, respectively).

Fig. 2A shows OS using a Kaplan-Meier curve, in which OS was superior in the IFN group than in the TKI group. Median OS in the IFN and TKI groups was 71 and 47
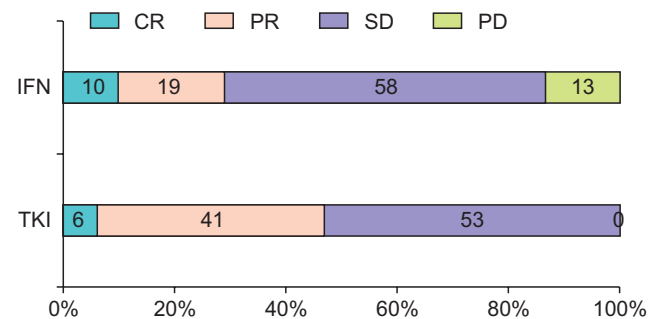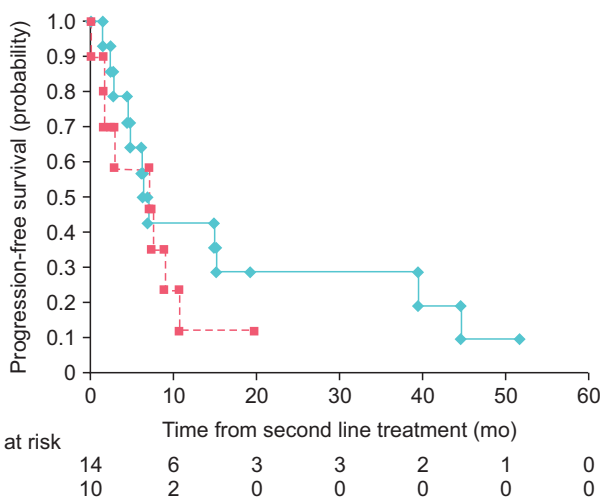

Fig. 1. Response rate to first-line therapy: interferon (IFN) (n=31), tyrosine kinase inhibitor (TKI) (n=17). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
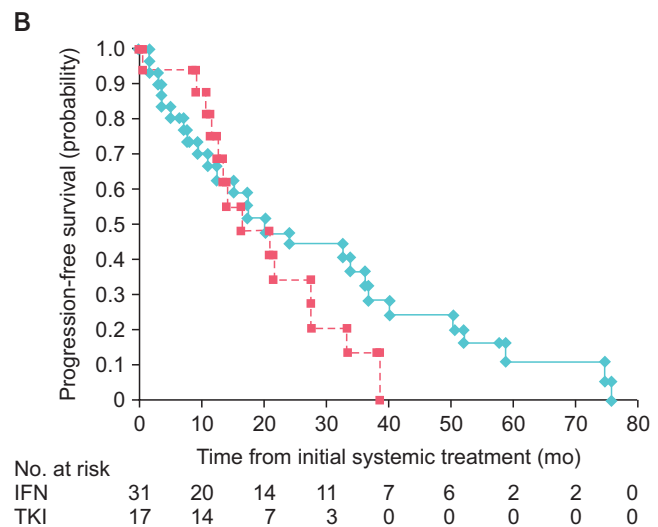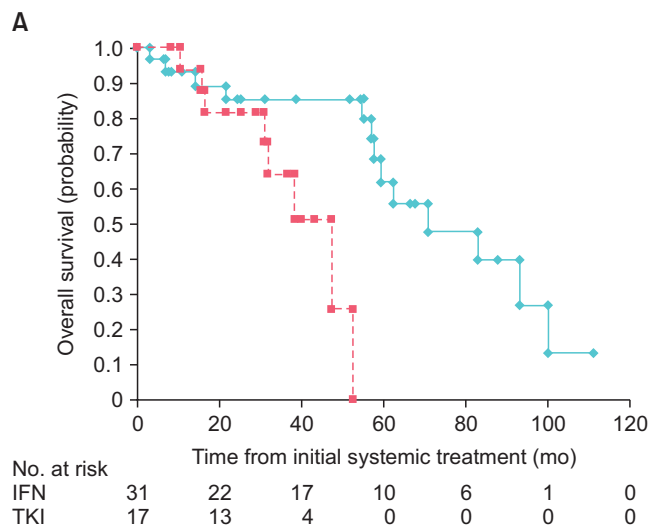
Fig. 2. (A) Kaplan-Meier curves of overall survival (p=0.014) and (B) progression-free survival (p=0.302) in patients who received interferon (IFN) or tyrosine kinase inhibitor (TKI) as first-line therapy for metastatic renal cell cancer. Solid line represents IFN and dotted line represents TKI.

months, respectively (p=0.014). There was no significant difference in PFS when comparing the two groups. Median PFS was 20 and 16 months in the IFN and TKI groups, respectively. In the first year after initial systemic therapy, PFS was superior in the TKI group when compared with the IFN group (Fig. 2B). The superior PFS of TKI in the first year might influence the response rate, as 13% of the IFN group had PD in response to initial systemic therapy. By contrast, PD did not occur in the TKI group.

Fig. 3 presents second-line PFS as a Kaplan-Meier curve. No significant difference was found when comparing the two groups. Median PFS in the first-line IFN group (n=14) and TKI group (n=10) was 7 months and 7 months,

respectively (p=0.380). Four patients from the first-line IFN group had been treated using interleukin-2 as a second-line therapy. One patient from the first-line TKI group had been treated with IFN as a second-line therapy. The others were treated with TKI as a second-line therapy. There was no significant difference in the number of favorable-risk mRCC patients receiving a second-line therapy on the basis of the selection of IFN or TKI as a first-line therapy in this study.

Fig. 4A presents OS on the basis of metastatic sites. In patients with lung or lymph node metastasis, no significant difference was found when comparing the first-line IFN and TKI groups. Median OS in the first-line IFN group (n=23) and TKI group (n=4) was 70 months and 16 months, respectively (p=0.230). Fig. 4B presents OS in patients with metastatic disease at sites other than the lung or lymph nodes. A significant difference was found in OS when comparing IFN or TKI as a first-line therapy. Median OS in the first-line IFN group (n=8) and TKI group (n=13) was 57 months and 47 months, respectively (p=0.032). These data suggest that first-line IFN therapy was not inferior to TKI therapy when evaluated according to metastatic sites.

DISCUSSION

This retrospective study showed that IFN was effective for MSKCC-defined favorable-risk mRCC patients. Median OS in the IFN group (71 months) was longer than that in the TKI group (47 months). Median PFS in the IFN group (20 months) was not significantly different
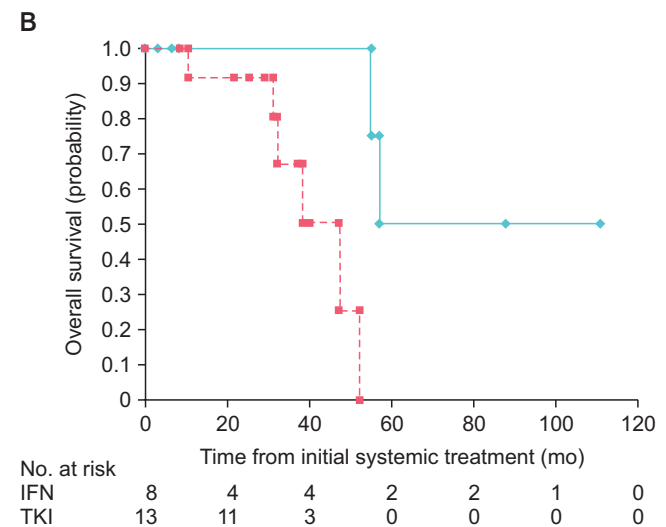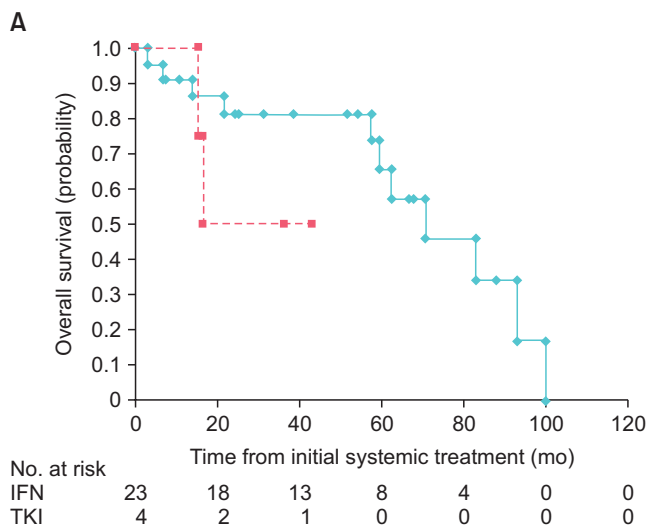

Fig. 3. Kaplan-Meier curves of second-line progression-free survival according to first-line therapy (p=0.380). Solid line represents first-line Interferon (IFN) and dotted line represents first-line tyrosine kinase inhibitor (TKI).

No. at risk						
IFN	14	6	3	3	2	1	0
TKI	10	2	0	0	0	0	0

No. at risk						
IFN	23	18	13	8	4	0	0
TKI	4	2	1	0	0	0	0

No. at risk						
IFN	8	4	4	2	2	1	0
TKI	13	11	3	0	0	0	0

Fig. 4. (A) Kaplan-Meier curves of overall survival in patients with lung and/or lymph nodes metastasis (p=0.230) and (B) in patients with metastatic disease at sites other than the lung or lymph nodes (p=0.032). Solid line represents Interferon (IFN) and dotted line represents tyrosine kinase inhibitor (TKI).

from that in the TKI group (16 months). There was no significant difference in PFS after second-line therapy on the basis of the selection of IFN or TKI as the first-line therapy. IFN was not inferior to TKI therapy according to metastatic sites. Three patients (10%) in the IFN group and two patients (12%) in the TKI group suffered from toxicities and could not continue IFN. Because they could not continue their primary systemic treatment, their metastasis led to progression. There was no significant difference in tolerability of the first-line therapies.

This study demonstrated a higher response rate in the IFN group (29%) than in the TKI group (47%). Response rates in the range of 30% to 40% have been observed in response to recent TKI treatment [8,9]. Furthermore, the response to IFN treatment seen in the present study is also superior to that seen in a previous report (10%–20%) [4,5]. It is possible that patients in previous reports included those with MSKCC-defined intermediate- and poor-risk disease as well as patients with a different distribution of ethnicity than in the present study.

A previous study of MSKCC risk classification in Japanese patients with mRCC showed that median OS was not reached and that 3-year OS was 80% among MSKCC-defined favorable-risk patients. Studies on Japanese mRCC patients have showed varying survival times compared with studies conducted on North American or European patients. However, there were some differences in the distribution of patients among the different risk groups and in the survival time according to risk group when comparing Japanese studies with other studies [10]. Another Japanese retrospective study of 1,467 patients with mRCC showed that OS was about 2 times longer than that seen in previous studies in North America and Europe in the cytokine era [3]. Therefore, Japanese mRCC patients might have better outcomes than do North American and European mRCC patients.

Cytokine treatment was previously the standard therapy for mRCC. IFN-alpha monotherapy is associated with an improvement in survival among patients with advanced RCC [11-13]. However, previous trials have not shown the superiority of cytokine treatment monotherapy over other therapies [14]. IFN-alpha was chosen as the comparator in several trials on the basis of data from previous studies and the widespread use of this agent.

Because IFN therapy is associated with a low response rate and substantial adverse effects, identification of reliable predictive markers for a favorable response to IFN is needed to establish optimal treatment strategies for patients with mRCC. A Japanese genetic study was the first prospective study to demonstrate that a STAT3 polymorphism can predict favorable response to treatment with IFN-alpha in patients with mRCC [6]. Another Japanese study demonstrated that the sensitivity to IFN-alpha is increased by YB-1 suppression and that this suppression does not downregulate IFN-alpha activation of T lymphocytes [15]. Further study should be performed to clarify the difference between Japanese mRCC patients and those from other geographic regions and ethnicities.

This study demonstrated that IFN was not inferior to TKI therapy according to metastatic sites. A previous Japanese study showed that it is possible to improve the success rate in treating advanced RCC patients, especially those with lung metastases, if combination therapy with interleukin-2 and IFN-alpha is chosen as the first-line treatment. That study showed an ORR of 35.5% and a clinical benefit rate of 80.6% in patients with lung metastasis alone; those values were 60.0% and 80.0%, respectively, in patients with lung plus lymph node metastasis. On the other hand, in patients with lung plus bone metastatic sites, the ORR was 33.3% and the clinical benefit rate was 33.3% [16]. Endpoint results from specific surveillance of sunitinib treatment of Japanese patients showed that the ORR for all MSKCC-defined risk groups was 22.8% for patients with lung metastasis, 18.9% for patients with liver metastasis, and 14.9% for patients with bone metastasis [17]. Endpoint results from specific surveillance of sorafenib treatment of Japanese patients showed that the ORR of all MSKCC-defined risk groups was 33.5% for patients with lung metastasis, 16.8% for patients with liver metastasis, 11.7% for patients with bone metastasis, and 12.5% for patients with brain metastasis [18]. These data demonstrated that patients with lung metastasis experience a better response than do other patients when treated with immunotherapy or TKI therapy. In the present study, the number of patients with metastatic disease was low, because the patient population consisted of those with MSKCC-defined favorable-risk disease, and this phenomenon might have affected the results. The present study and previous reports showed that TKI produces insufficient benefit in patients with metastatic disease at sites other than the lung or lymph nodes.

Because this was a retrospective study with a small number of patients treated with TKI for first-line systemic treatment, our understanding of the use of a single TKI agent for first-line systemic treatment is limited. In this study, administration of each TKI agent was affected by approval for clinical use. Recently, sunitinib and pazopanib

have been recommended for use as single TKI agents for first-line therapy of good- to intermediate-risk clear cell carcinoma on the basis of the results of large randomized clinical trials [1]. Further study is needed to determine appropriate first-line TKI agents in favorable-risk patients.

This retrospective study included patients with non–clear-cell histology in the IFN group. Patients with sarcomatoid variants and collecting duct RCC have poor survival [19]. In this group of enrolled patients, one patient with sarcomatoid carcinoma was alive and being treating with IFN 10 months after systemic treatment, whereas the other patient died 17 months after IFN treatment and PFS was 2.8 months. One patient with collecting duct carcinoma was dead 13 months after IFN treatment and PFS was 1.5 months, the other patient was alive at 68 months after IFN treatment and PFS was 50 months. In this study, some of the patients with a poor prognosis histology received a survival benefit. This seemed to be affected by good general condition and performance status. In the target therapy era, we might be able to achieve effectiveness in Japanese patients with non–clear-cell, favorable-risk disease treated with IFN. Further clinical study with a large number of patients is needed to clarify the treatment effects of IFN in non–clear-cell, favorable-risk patients.

This study was limited by the small number of enrolled patients. There is the possibility of bias in the initial stage and in the era of starting systemic therapy. Our understanding of this study in MSKCC favorable-risk mRCC is limited and needs to be developed further. Further research about the molecular differences between Japanese patients and those of other ethnicities may improve our understanding of why some mRCC patients in this study had markedly better responses to immunotherapy.

Further clinical study is needed to evaluate favorable-risk patients with regard to OS and PFS in the selection of a first-line systemic therapy. Few reports have focused on systemic therapy for favorable-risk patients. The number of MSKCC-defined favorable-risk patients was originally too small. Collaborative group studies might help to boost the numbers of patients with this rare favorable-risk profile who are available for study.

CONCLUSIONS

IFN is associated with a survival benefit in Japanese patients with favorable-risk metastatic RCC in the era of targeted therapy. However, because the present study was a retrospective analysis, there is the possibility of outside factors influencing the results at the initial stage and in the era of starting systemic therapy. Further prospective study is needed.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Escudier B, Porta C, Schmidinger M, Algaba F, Patard JJ, Khoo V, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 Suppl 3:iii49-56.

2. Hutson TE, Quinn DI. Cytokine therapy: a standard of care for metastatic renal cell carcinoma? Clin Genitourin Cancer 2005; 4:181-6.

3. Naito S, Yamamoto N, Takayama T, Muramoto M, Shinohara N, Nishiyama K, et al. Prognosis of Japanese metastatic renal cell carcinoma patients in the cytokine era: a cooperative group report of 1463 patients. Eur Urol 2010;57:317-25.

4. Klapper JA, Downey SG, Smith FO, Yang JC, Hughes MS, Kammula US, et al. High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma: a retrospective analysis of response and survival in patients treated in the surgery branch at the National Cancer Institute between 1986 and 2006. Cancer 2008;113:293-301.

5. Belldegrun AS, Klatte T, Shuch B, LaRochelle JC, Miller DC, Said JW, et al. Cancer-specific survival outcomes among patients treated during the cytokine era of kidney cancer (1989-2005): a benchmark for emerging targeted cancer therapies. Cancer 2008;113:2457-63.

6. Eto M, Kamba T, Miyake H, Fujisawa M, Kamai T, Uemura H, et al. STAT3 polymorphism can predict the response to interferon-α therapy in patients with metastatic renal cell carcinoma. Eur Urol 2013;63:745-52.

7. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002;20:289-96.

8. Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol 2006;24:16-24.

9. Motzer RJ, Rini BI, Bukowski RM, Curti BD, George DJ, Hudes GR, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006;295:2516-24.

10. Shinohara N, Abe T, Mochizuki T, Kashiwagi A, Kanagawa K, Maruyama S, et al. Is Memorial Sloan-Kettering Cancer Center risk classification appropriate for Japanese patients with metastatic renal cell carcinoma in the cytokine era? Urol Oncol 2013;31:1276-82.

11. Coppin C, Porzsolt F, Awa A, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. Cochrane Database Syst Rev 2005;(1):CD001425.

12. Medical Research Council Renal Cancer Collaborators. Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Lancet 1999;353:14-7.

13. Pyrhonen S, Salminen E, Ruutu M, Lehtonen T, Nurmi M, Tammela T, et al. Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. J Clin Oncol 1999;17:2859-67.

14. Negrier S, Gomez F, Douillard JY, Ravaud A, Chevreau C, Buclon M, et al. Prognostic factors of response or failure of treatment in patients with metastatic renal carcinomas treated by cytokines: a report from the Groupe Français d'Immunothérapie. World J Urol 2005;23:161-5.

15. Takeuchi A, Shiota M, Tatsugami K, Yokomizo A, Kuroiwa K, Dejima T, et al. YB-1 suppression induces STAT3 proteolysis and sensitizes renal cancer to interferon-α. Cancer Immunol Immunother 2013;62:517-27.

16. Akaza H, Kawai K, Tsukamoto T, Fujioka T, Tomita Y, Kitamura T, et al. Successful outcomes using combination therapy of interleukin-2 and interferon-alpha for renal cell carcinoma patients with lung metastasis. Jpn J Clin Oncol 2010;40:684-9.

17. Specific surveillance for Sunitinib of Japanese at final version (in Japanese) [Internet]. Tokyo: Pfizer Japan Inc.; c2015 [cited 2012 Mar 15]. Available from: http://pfizerpro.jp/cs/sv.

18. Specific surveillance for Sunitinib of Japanese at final version (in Japanese) [Internet]. Tokyo: Bayer Yakuhin Ltd.; c2015 [cited 2013 May 16]. Available from: http://www.nexavar.jp/unmember/pdf/rcc201305.

19. Keegan KA, Schupp CW, Chamie K, Hellenthal NJ, Evans CP, Koppie TM. Histopathology of surgically treated renal cell carcinoma: survival differences by subtype and stage. J Urol 2012;188:391-7.