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ORIGINAL ARTICLE

Sequential therapy and prognostic factors in metastatic renal cell carcinoma: single centre experience

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Summary

Purpose: *In advanced stage renal cell cancer (RCC), overall survival (OS) of patients has been prolonged due to targeted therapies. To date, there are several prognostic risk models that have been developed for metastatic RCC (mRCC). The purpose of this study was to evaluate the outcomes of the sequential therapy (IFN-a, tyrosine kinase inhibitors/TKIs, m-TOR inhibitor) and prognostic factors in patients with mRCC, especially those with bone metastasis.*

Methods: *We retrospectively examined the data of 82 patients with pathologically proven mRCC who were followed-up and treated at the Medical Oncology Clinic of the Dr A.Y Oncology Hospital between 2005 and 2013.*

Results: *Median OS was 23 months in all patients with mRCC and 20 months in patients treated with TKIs. According to MSKCC and HENG risk classifications, median OS differed between the groups (p=0.02, p<0.001, respectively). Median OS was lower in patients with isolated bone metastasis compared to those with lung metastasis (16 vs 24 months, p=0.25). Median OS improved with increasing number of sequential therapies (p=0.08).*

Conclusion: *This study confirmed the correlation between MSKCC and HENG risk models and survival data. Additionally, it was shown that increase of the number of therapeutic lines in sequential therapy prolonged survival and that bone metastases were negative prognostic factors.*

Key words: *prognostic factor, renal cell cancer, sequential therapy, survival*

Introduction

In advanced stage RCC, the introduction of targeted therapies, such as TKIs and mammalian target of rapamycin (mTOR) inhibitors, completely changed the therapeutic approach and the patient OS has been prolonged [1]. Sequential administration of the existing therapeutic modalities was demonstrated to contribute to improvement of OS [2]. According to the American Joint Committee on Cancer (AJCC) TNM stage, 5-year survival rates were 81, 74, 53 and 8% for stage I, II, III and IV, respectively [3]. To date, there are several prognostic risk models that have been developed for mRCC [4,5]. In these models, bone metastasis was not included, but a recent study reported worse therapeutic outcomes for this patient group [6].

This study aimed to evaluate the outcomes of sequential therapy (IFN-α, TKIs and m-TOR inhibitor therapy) and prognostic factors, especially in patients with mRCC and bone metastasis.

Methods

We retrospectively examined the data of 82 patients histopathologically diagnosed with mRCC between 2005 and 2013, who were treated and followed-up at the Medical Oncology Clinic of Dr A.Y Oncology Hospital. Patient clinicopathological characteristics and therapeutic data were registered from their medical records. In our country, for patients with

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mRCC, the administration of first-line IFN-α therapy is mandatory. Response was evaluated by using the Response Evaluation Criteria in Solid Tumors (RECIST). Demographic and clinical characteristics were summarised using median, range or counts and frequencies as appropriate.

Definitions

Progression-free survival (PFS) was defined as the time (in months) from diagnosis to clinical progression, death or, if none of these occurred, the last follow-up date. OS was calculated from the initiation of therapy to death from any cause or to the date of last contact.

Statistics

Statistical analysis was performed using Student's t-test and Pearson's chi-square test for parametric and Mann-Whitney U test for non-parametric analysis. The survival of patients was estimated using the Kaplan-Meier method with log rank test and factors that might affect survival were assessed using Cox uni - and multivariate regression analysis. Results were considered significant when two-sided p values were <0.05. For statistical analysis, SPSS for Windows, version 15.0 software (SPSS Inc., Chicago, Ill, USA) was used.

Results

Demographics and therapeutic modalities

The male to female ratio was 2.7 and the patient median age was 57 years (range 21-87). According to the pathological subgroups, 50 (60.9%) patients had clear cell carcinoma, 8 (9.7%) had papillary carcinoma and 2 (2.4%) had chromophobe-type carcinoma. In 22 (26.8%) patients, no subgroup was reported. In 4 (4.8%) patients, sarcomatoid differentiation was observed. While 38 (46.4%)patients had stage 4 disease at the time of diagnosis, 44 (53.6%) patients developed metastasis during follow-up after primary surgery in the early stages of disease; in this group, the median time to metastasis was 24 months (range 0-204). Time to metastasis was ≤ 12 months in 52 (63.4%) patients and >12 months in 30 (36.5%). Metastatic sites were found in the lung in 34 (40.9%) patients, bone in 14 (16.8) patients, lung and brain in 8 patients (9.6%), lung and bone in 6 patients (7.2%), lung and liver in 8 (9.6%) patients and intra-abdominal and mediastinal lymph nodes in 13 (15.6%) patients. Of a total of 82 patients, 13 (15.7%) did not undergo nephrectomy. When 82 metastatic patients were examined for MSKCC risk factors, 20 (24.3%) were classified as low-risk, 48 (58.5%) as intermediate-risk and 14 (17%) as high-risk. According to HENG risk factors, 21 (25.6%) patients were classified as low-risk, 47 (57.3%) as intermediate-risk and 14 (17%) as high-risk. Patient characteristics are summarised in Table 1.

After analysis of the therapeutic modalities administered to 82 metastatic patients, 76 (92.6%) received first-line IFN-α therapy and 62 (75.6%) received second-line TKI therapy. When the patients treated with TKI were divided into subgroups, 52 (83.9%) patients were adminsitered sunitinib, 7 (11.3%) sorafenib and 3 (4.8%) pazopanib. Of the patients who progressed on TKI therapy, 11 (55%)

Table 1. Patient characteristics

Characteristics	*Number of patients (%)*
Gender	
Male	60 (73.1)
Female	22 (26.8)
Age, years, median (range)	57 (21-87)
ECOG PS	
0-1	48 (59)
2-3	34 (41)
Nephrectomy	
Yes	69 (84.1)
No	13 (15.8)
Sarcomatoid differentiation	4 (4.8)
Pathological stage at diagnosis	
1	2 (2.4)
2	26 (31.7)
3	16 (19.5)
4	38 (46.3)
Metastasis time ≤ 12 months	52 (63.4)
Metastasis time > 12 months	30 (36.5)
Time to metastasis (months, range)	24 (0-204)
MKCC risk factors	
Low risk	20 (24.3)
Moderate risk	48 (58.5)
High risk	14 (17).
HENG risk factors	
Low risk	21 (25.6)
Moderate risk	47 (57.3)
High risk	14 (17)
Metastatic sites	
Lung	34 (40.9)
Bone	14 (16.8)
Lung+brain	8 (9.6)
Lung+bone	6 (7.2)
Lung+liver	8 (9.6)
Other	13 (15.6)
Number of metastases	
Solitary	3 (3.6)
Multiple	79 (96.4)
Number of therapies received	
None	7 (8.5)
One line	15 (18.2)
Two lines	49 (59.7)
Three lines	8 (9.7)
Four lines	3 (3.6)

Table 2. Therapeutic modalities

Treatment modality	*N (%)*
IFN-α therapy	
Yes	76 (92.6)
No	6 (7.3)
Response to IFN-α	
Intolerance	23 (30.3)
Stable disease	8 (10.5)
Progression	45 (49.2)
Progression sites	
Lung	25 (55.5)
Brain	5 (11.1)
Bone	5 (11.1)
Abdominal lymphadenopathy	5 (11.1)
Liver	3 (6.6)
Lung + brain	1 (2.2)
Spleen	1 (2.2)
IFN-α side effects	
No	19 (25)
Influenza-like syndrome	41 (53.9)
Fatigue	14 (18.4)
Diarrhea	1 (1.3)
Fatigue+proteinuria	1 (1.3)
Side effect grades	
Unknown	2 (2.6)
Grade 1	3 (30)
Grade 2	30 (39.4)
Grade 3	20 (26.3)
Grade 4	2 (2.6)
TKI therapy	
Yes	62 (75.6)
No	20 (24.3)
TKI subgroups	
Sunitinib	52 (83.9)
Sorafenib	7 (11.3)
Pazopanib	3 (4.8)

Treatment modality	*N (%)*
Response to TKI therapy	
Intolerance	6 (11.2)
Stable disease	30 (48.4)
Partial response	6 (9.79)
Progression	20 (32.3)
Progression sites	
Lung	13 (65)
Brain	1 (5)
Bone	3 (15)
Abdominal lymphadenopathy	1 (5)
Skin	1 (5)
Lung + brain	1 (5)
TKI side effects	
No	8 (13)
Yes	54 (87)
a) Hypertension	9 (14.5)
b) Fatigue	19 (30.6)
c) Hypothyroidism	11 (17.7)
d) Hand-foot syndrome	15 (24.1)
e) Neutropenia	7 (11.2)
f) Thrombocytopenia	3 (4.8)
g) Diarrhea	1 (1.6)
Side effect grades	
Unknown	4 (7.4)
Grade 1	1 (1.8)
Grade 2	40 (74)
Grade 3	8 (14.8)
Grade 4	1 (1.8)
Treatment after TKI therapy	
No	9 (45)
Yes (everolimus)	11 (55)
Response to everolimus	
Progression	7 (63)
Stable	4 (36.4)
Everolimus side effects	
No	10 (91)
Yes (pneumonitis)	1 (9)

were given third-line therapy with the mTOR inhibitor everolimus. In 3 patients who developed progression on everolimus, axitinib therapy was initiated.

The side effects most commonly seen were grade 2 and 3 flu-like syndrome and fatigue and grade 2 fatigue, hypothyroidism and hand-foot syndrome in patients treated with TKI. Only one of the 10 patients treated with everolimus experienced pneumonitis. Therapeutic modalities are summarised in Table 2.

Survival analysis

Of 82 patients with mRCC, 76 (92.6%) received IFN-α therapy, whereas 6 (7.3%) did not receive any therapy. Median PFS was 2 months (95% CI:1.32-2.67). In patients who received TKI, median PFS was 11 months (95% CI:6.81-15.18). According to MSKCC, among the patients treated with TKI, median PFS was 19 months in the low-risk group, 8 months in the intermediate-risk group and 3 months in the high-risk group (p=0.048). According to HENG, among the patients treated with TKI, median PFS was not reached in the low-risk group, whereas it was 8 months in the intermediate-risk group and 3 months in the high-risk group (p=0.001). In patients treated with everolimus, median PFS was 4 months (95% CI:1.26-6.73). Median OS was not reached.

In a total of 82 patients with mRCC, OS was 23 months (95% CI:9.06-36.93). In patients who were administered TKI, median OS was 20 months (95% CI:6.58-33.41). According to MSKCC, median OS was not reached in the low-risk group, while it was 18 months in the intermediate-risk group and 8 months in the high-risk group (p=0.02). According to HENG, median OS was not reached in the low-risk group, whereas it was 18 months in the intermediate-risk group and 8 months in the high-risk group (p<0.001).

In patients with tumors of sarcomatoid differentiation, OS was lower compared to other groups but without statistical significance (7 vs 23 months, p=0.2). Median OS was lower in patients with isolated bone metastasis compared to those with lung metastasis (16 vs 24 months, p=0.25). Furthermore, when the patients were classified according to the presence of bone metastasis, it was seen that the presence of bone metastasis correlated with shorter survival, but this was not statistically significant (p=0.9). When the patients were analysed in relation to the number of therapies received, it was seen that, although statistical significance was not reached between the groups, the median OS was extended with increasing number of therapies (p=0.08) (Tables 3,4).

With regard to patient characteristics, those with a negative effect on OS included absence of previous nephrectomy (p=0.002), capsule invasion (p=0.009), lymphovascular invasion (p=0.029), time to metastasis ≤12 months (p=0.001) and ECOG PS (p=0.015).

Discussion

In the treatment of early-stage RCC the gold standard of therapy is nephrectomy [7,8]. In metastatic disease, nephrectomy was reported to contribute positively to OS [9]. In our data, OS was 32 months in patients who underwent nephrectomy and 14 months in those who did not (p=0.002).

Alternative therapeutic modalities for the treatment of RCC depend on actual guidelines as well as the social security institutions of the different countries; these therapies include high-dose IL-2, IFN-α, bevacizumab and IFN-α combination, TKI, and mTOR inhibitors in mRCC patients with good PS [10].

In mRCC, the overall response rate to IFN-α monotherapy is about 15% and the median duration of response about 4 months [11]. In as study 463 patients diagnosed with mRCC according to MSCKK and treated with IFN-α were retrospectively analysed; the median OS was 13 months and PFS 4.7 months [12]. In our country, administration of first-line IFN-α therapy is mandatory in patients with mRCC. In our study, median PFS was 2 months, which is lower than PFS reported in the literature. This may be explained by the fact that, in these patients, the physician requested that they should switch to TKI therapy. Consequently, starting first-line therapy using TKIs would provide better patient survival outcomes.

According to our data, patients who developed intolerance or disease progression after IFN-α therapy were given TKI as a second-line therapy. When TKI subgroups were considered, 52 (83.9%) patients received sunitinib, 7 (11.3%) sorafenib and 3 (4.8%) pazopanib.

In all of the groups treated with TKIs, PFS and OS were 11 and 20 months, respectively. In both MSKCC and HENG classifications, when the groups were examined according to risk factors, a statistically significant difference was found between the groups (PFS p=0.04 and p=0.001, respectively; OS p=0.02 and p<0.001, respectively).

The phase 3 study of Motzer et al., which compared sunitinib vs IFN-α in the first-line treatment

Table 3. Comparison of survival rates between the two groups

Patient characteristics	*OS (months)*	*log rank, p*
All patients	23	0.6
Females	16	
Males	32	
Nephrectomy - present	32	0.002
Nephrectomy - absent	14	
ECOG PS		0.015
Baseline pathological stage		0.02
Furhman grade		0.41
Pathological subgroup		0.7
Clear cell	23	
Papillary	22	
Unknown subgroup	23	
Sarcomatoid differentation		0.2
Yes	7	
No	23	
Metastatic sites		0.25
Lung	24	
Bone	16	
Lung+brain	20	
Lung+bone	20	
Lung+liver	8	
Other	Not reached	
Bone metastasis		0.9
Yes	20	
No	26	
Time to metastasis (months)		0.001
≤12	16	
>12	36	
MSKCC risk factor		0.001
Low risk	Not reached	
Moderate risk	19	
High risk	4	
HENG risk factor		<0.001
Low risk	Not reached	
Moderate risk	20	
High risk	4	
TKI side effects		0.55
Yes	23	
No	18	

Table 4. Survival results by therapeutic modality

Therapeutic modalities	*PFS (months)*	*log rank, p*	*OS (months)*	*log rank, p*
All patients treated with IFN-a	2			
IFN-a MSKCC risk factor		0.003		
Low risk	2			
Moderate risk	3			
High risk	1			
IFN-a HENG risk factor		0.001		
Low risk	2			
Moderate risk	2			
High risk	1			
All patients treated with TKI	11		20	
TKI MSKCC risk factor		0.048		0.02
Low risk	19		Not reached	
Moderate risk	8		18	
High risk	3		8	
TKI HENG risk factor		0.001		<0.001
Low risk	Not reached		Not reached	
Moderate risk	8		18	
High risk	3		8	
Sunitinib	10	0.2	23	0.7
Sorafenib	13		19	
Sunitinib MSKCC risk factor		0.11		0.047
Low risk	Not reached		Not reached	
Moderate risk	9		18	
High risk	14		8	
Sunitinib HENG risk factor		0.03		0.001
Low risk	17		Not reached	
Moderate risk	10		20	
High risk	9		8	
Sorafenib MSKCC risk factor	Inadequate events	0.68	Inadequate events	0.68
Sorafenib HENG risk factor	Inadequate events	0.68	Inadequate events	0.42
Patients treated with m-TOR	4		Not reached	
Number of therapies received				0.08
None	11			
One line	16			
Two lines	20			
Three lines	26			
Four lines	32			

of patients with mRCC with good or intermediate prognosis (N=750), the response rate (47 vs 12%), median PFS (11 vs 5 months) and OS (26.4 vs 21.8 months) were in favor of the sunitinib arm [13,14]. According to our data, in 52 patients treated with sunitinib, PFS was 10 months and OS 23 months. Patients treated with sunitinib were classified by MSKCC and HENG risk factors and it was observed that PFS did not show a statistically significant difference according to MSKCC risk classification but a statistically significant difference was observed according to HENG classification (p=0.068, p=0.003). In the OS analysis, statistical significance was found with both risk classifications (p=0.019, p<0.001). The use of HENG classification in patients treated with TKI therapy was more significant [15].

In our study, the group treated with sorafenib had a median PFS of 13 months and OS of 19 months. The small number of patients precluded their categorization according to risk models for PFS and OS. Unlike the reports in the literature, PFS was prolonged. PFS for sorafenib was not found to be a reliable indicator, due to the small number of patients and the use of cytokine therapy for a too short period of time in the majority of the patients. In the phase 3 TARGET study conducted on patients with mRCC, who had been previously treated and developed progression, the patients were randomised to sorafenib and placebo arms [16-18]. Median PFS was significantly longer in favor of sorafenib, with 5.5 months vs 2.8 months. Although not statistically significant, OS was 17.8 months vs 15.2 months in the sorafenib

and placebo arms, respectively [17]. In the recent INTORSECT study, second-line sorafenib therapy resulted in an OS of 16 months and a PFS of 3.9 months. The sunitib and sorafenib arms did not show statistically significant difference in terms of PFS and OS (p=0.2 and p=0.7, respectively).

As only 3 of our patients received pazopanib therapy, no additional survival analysis was performed. In a phase 3 study conducted on 435 patients with mRCC, which compared pazopanib and placebo, PFS was significantly longer in the pazopanib arm with 9.2 months vs 4.2 months in the placebo group [19,20]. The PISCES study is a phase 3 study conducted to compare pazopanib and sunitinib in terms of tolerance [21]. Pazopanib resulted in better quality of life. In our study, as the number of patients treated with pazopanib was limited, the differences in the side effects between TKIs were not investigated. In our study, when the side effects observed in the patients treated with TKI were examined, no statistical significance was found between the side effects of TKI and OS (p=0.55).

In patients with mRCC, second-line axitinib and everolimus treatment has been approved. At the start of this study, in our country, only everolimus given after TKI had been approved; however, during the last period of the study, those patients who showed progression after everolimus therapy were able to receive axitinib upon out-of-indication application. In our study, patients who showed disease progression after TKI therapy, everolimus therapy resulted in a median PFS equal to 4 months, whereas OS was not reached. In a phase 3 study conducted on 410 patients with mRCC, patients were assigned to everolimus (10 mg/day) or placebo arms [22,23]. PFS was significantly longer in the everolimus arm (median 4.9 vs 1.9 months). No benefit was demonstrated for OS (14.8 vs 14.4 months). The incidence of side effects such as stomatitis and pneumonitis was higher in the everolimus arm (3 vs 0% and 3 vs 0%, respectively). In our data median OS was not reached and PFS was similar to the values reported in the literature. One patient (9%) showed pneumonitis as side effect.

In the second-line phase 3 AXIS study, patients with mRCC were divided into axitinib and sorafenib arms [24]. In this study, axitinib was superior to sorafenib in patients who had been previously treated with cytokine therapy. In 3 patients who showed disease progression after therapy with everolimus, axitinib therapy was initiated. However, as a sufficient follow-up time was not reached in these patients, PFS and OS analysis was not performed.

In our study, when the number of therapies administered to the patients was examined, it was found that, despite the lack of any statistical significance across the groups, increasing the number of therapies prolonged the median OS. In the study conducted by Soerensen et al., similar results were obtained which reached statistical significance [2].

Time to metastasis has no effect on OS. In MSKCC and HENG risk models, time to metastasis was used as a risk factor [4,5]. In our study, OS was 16 months in patients with time to metastasis <12 months vs 36 months in the patients with time to metastasis >12 months; this difference was statistically significant (p=0.001).

A negative correlation was reported between ECOG PS and OS [4,25] and a similar correlation was also detected in our study (p=0.015). In previous studies, OS was higher in patients with clear cell carcinoma compared to other subgroups [2]. In our study, pathological subgroup analysis revealed that OS was not different across the pathological groups (p=0.7), probably due to the small number of patients of the other subgroups besides clear cell carcinoma. Similar to previous studies, our analysis revealed that the incidence rates were 40.9% for lung metastasis, 16.8% for bone metastasis, 9.6% for liver metastasis and 9.6% for brain metastasis [26-29].

Despite the lack of statistically significant difference between metastatic sites and OS, the median OS was lower in patients with isolated bone metastasis compared to those with lung metastasis (16 vs 24 months, respectively; p=0.25). Median OS was lower in patients with bone metastasis compared to those without (20 vs 26 months, p=0.9), and the lowest OS was seen in patients with lung and liver metastases, with OS of 8 months. In the study conducted in Belgium-France (N=223), it was found that bone metastasis (HR 0.46; p<0.0001) and increased platelet count (>400,000/mm^3) (HR 0.60; p=0.03) were independent risk factors for PFS, while bone metastasis (HR 0.48; p=0.001) and ECOG PS >0 (HR 0.54; p=0.008) were independent risk factors for OS. In this study, PFS was 8.2 months in patients with bone metastasis vs 19.1 months in those without (p<0.0001) and OS was 19.5 months in patients with bone metastasis vs 38.5 months in those without (p<0.0001) [6].

Limitations of the present study include its retrospective design and the small number of pa-

tients in the sorafenib and pazopanib arms.

This study allowed confirmation of the correlation between MSKCC and HENG risk models and survival data, which have been previously demonstrated. Furthermore, nephrectomy was shown to positively increase survival. Also, it was demonstrated that increasing the number of therapeutic lines in sequential therapy prolonged OS, and bone metastases were negative prognostic factors.

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