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ORIGINAL ARTICLE

Minoru Kobayashi · Hitoshi Ikeda · Akinori Nukui
Kazumi Suzuki · Yasuhiro Sugaya · Masayuki Yuzawa
Tatsuo Morita

Clinical outcome and prognostic survival factors in patients with advanced renal cell carcinoma treated with very low-dose interleukin-2, interferon-α, and tegafur-uracil: a single-institution experience

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Abstract
Background. The objective of the current study was to determine the efficacy and safety of very low-dose interleukin-2 (IL-2), interferon (IFN)-α, and tegafur-uracil for patients with unresectable renal cell carcinoma (RCC), metastatic RCC, or both. Clinical prognostic factors were also investigated.
Methods. Fifty consecutive patients underwent a 3-week treatment cycle of IL-2 (0.7×10^6 Japanese reference units [JRU])/person on days 1–3 weekly), IFN-α (3×10^6 international units/person, on days 1–5 weekly), and tegafur-uracil (300 mg/person daily).
Results. The median follow-up after treatment initiation was 11.3 months. A median of three (range, 1–20) treatment cycles was administered. Of 47 eligible patients, 4 had a treatment response (3 complete responses and 1 partial response; objective response rate, 8.5%). The median progression-free and overall survivals were 8.3 months (95% confidence interval [CI], 5.5–10.9 months) and 38.8 months (95% CI, 27.8–49.7 months), respectively. Only 8 patients had grade III/IV toxicities. Two parameters, i.e., the absence of a previous nephrectomy and a low hemoglobin level, were identified as independent factors predictive of poor survival. Patients with low or intermediate risk (presence of none or one of the two prognostic factors) had a durable median survival exceeding 30 months. High-risk patients with both risk factors had rapid disease progression despite treatment.
Conclusion. While the effectiveness of this immunochemotherapy resulted in a limited antitumor response, low- and intermediate-risk patients with metastatic RCC seemed likely to have a survival benefit. Patient selection is essential to enhance treatment efficiency and avoid useless treatment for high-risk patients.

M. Kobayashi (✉) · H. Ikeda · A. Nukui · K. Suzuki · Y. Sugaya · M. Yuzawa · T. Morita
Department of Urology, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan
Tel. +81-285-58-7379; Fax +81-285-40-6595
e-mail: minoruk@jichi.ac.jp

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Introduction

Metastatic renal cell carcinoma (RCC) is resistant to chemotherapy and irradiation, and, therefore, various immunotherapeutic strategies have been evaluated for patients with advanced RCC.[1] Several studies have focused on combined treatment with interferon (IFN)-α and interleukin-2 (IL-2), suggesting a therapeutic advantage compared with treatment with either agent alone.[2–5] Despite the initial encouraging results with high-dose IL-2, this regimen has not become common because of its considerable toxicity and associated fatalities.[2,4,6,7] In contrast, lower-dose IL-2, in combination with IFN-α, showed efficacy similar to that of the high-dose regimen, with substantially less toxicity.[8–11] In addition, the concomitant use of chemotherapeutic agents, notably 5-fluorouracil (5-FU), further enhanced the antineoplastic activity of cytokine treatment in RCC.[12,13]

The recommended dose of IL-2 in Japan is 0.7 to 2.1 Japanese reference units (JRU)/person daily, which was determined by a phase II clinical trial with a response rate of 15.4%.[14] The JRU is equivalent to the international unit (IU) and this range is markedly lower than the standard dose used in the United States and Europe.

Tegafur-uracil (UFT; Taiho Pharmaceutical, Tokyo, Japan) is an oral antineoplastic drug comprised of uracil and tegafur (a prodrug of 5-FU). We used this drug in combination with IFN-α to treat patients with metastatic RCC, expecting that the antineoplastic effects of 5-FU could be enhanced via biochemical modulation by IFN-α.[15,16] We proposed an immunochemotherapeutic regimen consisting of low-dose IL-2, IFN-α, and tegafur-uracil for patients with metastatic RCC.

In the present study, we analyzed the clinical effect of this immunochemotherapy on metastatic RCC. In addition, possible prognostic factors for disease progression and overall survival were analyzed in patients who received this

immunochemotherapy to identify candidates who might benefit from this treatment.

Patients and methods

Patients

Fifty patients with locally advanced RCC, metastatic RCC, or both, received immunochemotherapy at Jichi Medical University Hospital between 1999 and 2006. The patients were required to have measurable lesions, an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or less, estimated survival of 3 months or longer, and no severe complications. Of these patients, 47 patients (39 men, 8 women; median age, 63 years; range, 35–78 years) for whom sufficient follow-up data were available were evaluated. Nephrectomy was not performed in 11 (23.4%) patients because of bilateral or advanced primary disease sites. Thirteen (27.6%) patients had been resistant to previous IFN-α monotherapy. Informed consent to perform this study was obtained from all patients, and the study was approved by the research ethics committee of Jichi Medical University.

Immunochemotherapy

Immunochemotherapy was administered in 3-week cycles. IL-2 (Teceleukin, recombinant product; Shionogi, Osaka, Japan) was administered by subcutaneous infusion at a dose of 0.7×10^6 JRU)/person on days 1–3 weekly. IFN-α (Sumiferon, a natural type product; Sumitomo Pharmaceuticals, Osaka, Japan) was administered intramuscularly at a dose of 3×10^6 IU/person on days 1–5 weekly. Tegafur-uracil was given orally at a dose of 300 mg/person daily. This treatment cycle was repeated until obvious disease progression occurred.

The response to treatment was evaluated according to the World Health Organization (WHO) criteria after two to three cycles of treatment. Toxicity was evaluated on the basis of the WHO handbook for reporting results of cancer treatment.[17]

Prognostic factor analysis

All potential prognostic factors were transformed into categorical form as follows. The clinical features regarded as prognostic factors were: age (<63 vs ≥63 years), ECOG performance status (<2 vs ≥2), previous nephrectomy (yes vs no), metastasis at initial diagnosis (yes vs no), number of involved organs (single vs multiple), sites of metastases (lung alone vs others), occurrence of metastasis 1 year after nephrectomy (yes vs no), and previous IFN monotherapy (yes vs no). In addition, the following baseline biochemical parameters, previously reported as predictive of survival,[12,18,19] were also included: hemoglobin (≤11.5 g/dl [women]; ≤13.0 g/dl [men] vs >11.5 g/dl [women]; >13.0 g/dl [men]), lactate dehydrogenase (≤360 IU/l vs >360 IU/l), C-reactive protein (≤0.35 mg/ml vs >0.35 mg/ml), and immunosuppressive acid protein (≤500 μg/ml vs >500 μg/ml). The values in the patients are shown in Table 1.

Table 1. Patients' characteristics

Clinical factors	No. of patients
Age (years)	
<63	23
≥63	24
PS[a]	
<2	25
≥2	22
Previous nephrectomy	
Yes	36
No	11
Metastases at diagnosis	
Yes	18
No	29
Number of organs involved in metastases	
Single	20
Multiple	27
Lung metastasis alone	
Yes	13
No	34
Previous IFN therapy	
Yes	13
No	34
Hemoglobin(g/dl)	
≤13.0 (Male)	18
≤11.5 (Female)	1
>13.0 (Male)	21
>11.5 (Female)	7
Lactate dehydrogenase (IU/l)	
≤360	36
>360	11
C-reactive protein (mg/ml)	
≤0.35	20
>0.35	27
IAP (μg/ml)	
≤500	21
>500	26

[a] Eastern Cooperative Oncology Group (ECOG) performance status

Survival was estimated according to the Kaplan-Meier method, and the differences between survival curves were assessed using the log-rank test. The proposed prognostic parameters that were significantly associated with disease progression or survival, at $P < 0.10$, were included in a forward stepwise Cox's proportional-hazards regression model. $P < 0.05$ was considered statistically significant.

Results

Clinical effects

The median follow-up period after initiation of treatment was 11.3 months. A median of three cycles (range, 1–20) of treatment were administered. Of the 47 eligible patients, 3 patients (6.4%) achieved a complete response and 1 patient (2.1%) had a partial response, yielding an objective response rate of 8.5%. Eleven patients (23.4%) had stable disease, and 32 patients (68.1%) had progressive disease. Overall,

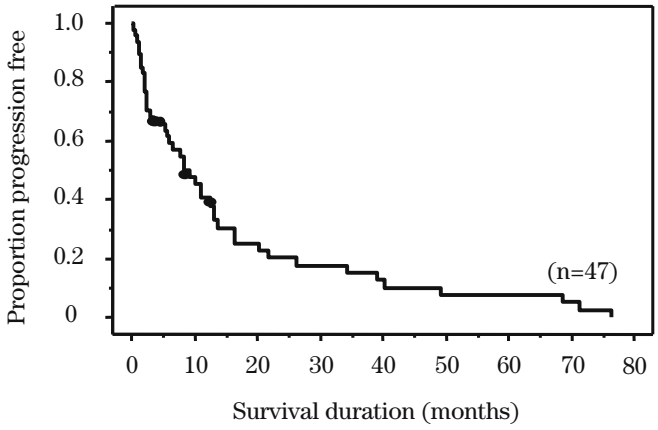

Fig. 1. Progression-free survival curve, by Kaplan-Meier estimates

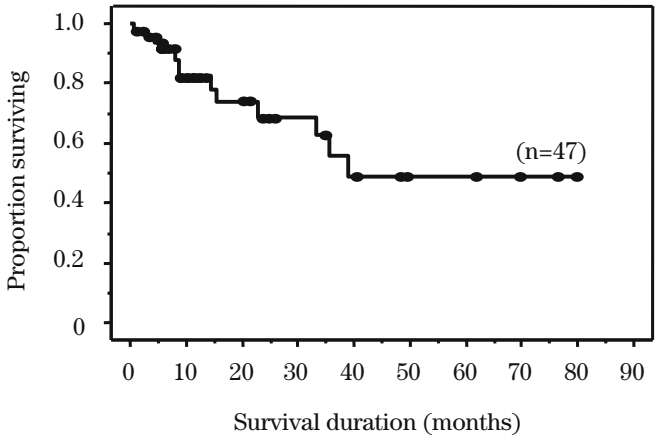

Fig. 2. Overall survival curve, by Kaplan-Meier estimates

disease stabilization, including complete and partial responses, was observed in 15 patients (31.9%).

The progression-free survival curve is shown in Fig. 1. The median progression-free survival was 8.3 months (range, 1–76 months; 95% confidence interval [CI], 5.5–10.9 months). The 1- and 3-year progression-free survival rates were 40.5% and 15.2%, respectively.

Figure 2 shows the overall survival curve. Thirty-four patients (72.3%) remained alive, and the overall survival rate at last follow-up was 48.7%. The median survival time was 38.8 months (range, 1–79 months; 95% CI, 27.8–49.7 months). All patients with stable disease were alive at the end of follow-up and had significantly better survival than those with progressive disease ($P = 0.006$). However, even patients with progressive disease had a median survival time of 33 months (range, 1–38 months; 95% CI, 18.5–47.8 months; Fig. 3).

Factors predictive of progression and survival after immunochemotherapy

On univariate analysis, the factors significantly associated with rapid disease progression were a higher performance

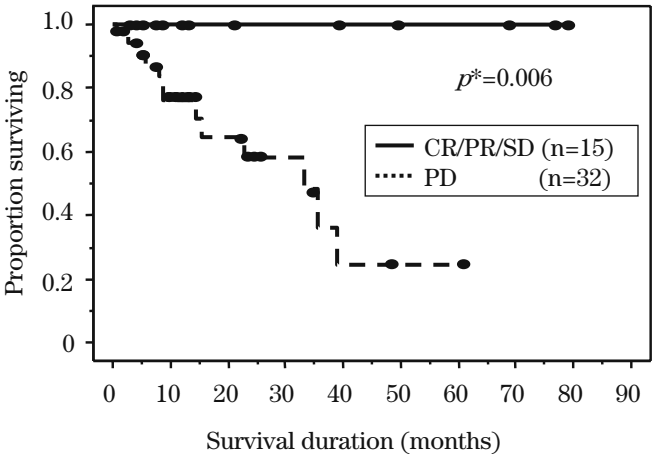

Fig. 3. Overall survival curves according to treatment response, by Kaplan-Meier estimates. The patients who achieved disease stabilization, including those who showed complete response (*CR*), partial response (*PR*), and stable disease (*SD*), survived significantly longer than those with progressive disease (*PD*). ($P = 0.006$, by log-rank test)

status ($P < 0.05$), the absence of a previous nephrectomy ($P < 0.05$), the presence of metastasis at diagnosis ($P < 0.01$), and an elevated C-reactive protein level ($P < 0.05$). These parameters were then included in a forward stepwise Cox multivariate analysis. Only the presence of metastasis at diagnosis remained as an independent predictive factor for disease progression ($P < 0.01$).

Univariate analysis was performed to identify factors predictive of survival after treatment. Factors significantly associated with a limited survival time were the absence of a previous nephrectomy ($P < 0.01$), the presence of metastasis at diagnosis ($P < 0.01$), and a low hemoglobin level ($P < 0.05$). On multivariate analysis, the absence of a previous nephrectomy ($P < 0.01$) and a low hemoglobin level ($P < 0.05$) remained as independent factors predictive of survival (Table 2).

Based on the sum of the two independent risk factors for survival, patients were assigned to the following groups: low-risk (no risk factor; $n = 24$), intermediate-risk (one risk factor; $n = 16$), or high-risk (two risk factors; $n = 7$). The median overall survival for patients in the low- and intermediate-risk groups was not reached at the time of censorship, while patients in the high-risk group had a median survival of 5.6 months (range, 1–12 months; 95% CI, 0.8–10.2 months). The patients in the high-risk group had a significantly shorter survival time compared with those in the low-risk and intermediate-risk groups ($P < 0.001$; Fig. 4).

Treatment toxicity

Overall, the treatment was well tolerated, and most adverse effects (consisting primarily of fever, mucositis, liver damage, and leucopenia) were limited to WHO grades 1 and 2 (Table 3). Either IL-2 or tegafur-uracil was discontinued in five patients due to grade 3/4 toxicity. No treatment-related deaths occurred.

Table 2. Significant prognostic factors for disease progression and overall survival

Prognostic factors	Disease progression				Overall survival			
	Univariate[a]	Multivariate[b]			Univariate[a]	Multivariate[b]		
	P value	Hazard ratio	95% CI	*P* value	*P* value	Hazard ratio	95% CI	*P* value
Performance status	0.0306	0.49	0.26–0.95	0.8269	0.1021	–	–	–
Previous nephrectomy	0.0252	2.28	1.08–4.81	0.8914	0.0015	5.96	1.73–2.04	0.0081
Metastasis at diagnosis	0.0002	3.25	1.68–6.28	0.0005	0.0093	4.05	1.25–1.31	0.1745
Hemoglobin level	0.2049	–	–	–	0.0263	3.52	1.08–1.15	0.0495
C-reactive protein level	0.0388	0.52	0.27–0.98	0.6182	0.2061	–	–	–

[a] Log-rank test
[b] Cox's proportional-hazards regression model

Table 3. Toxicities

Toxicities[a]	No. of patients		Incidence (%)
	Grades 1 and 2	Grades 3 and 4	Grades 1–4
Fever/chills	17	0	36.1
Nausea/vomiting	5	1	12.7
Diarrhea	2	1	6.4
Mucositis	4	2	12.7
Skin	2	0	4.3
CNS symptoms/disorientation	2	1	6.4
Vision problems	1	0	2.1
Headache	1	0	2.1
Leukocytopenia	5	1	12.8
Hemoglobinemia	0	2	4.3
Thrombocytopenia	1	0	2.1
Liver damage	5	0	10.6
Renal insufficiency	2	0	4.3

[a] World Health Organization (WHO) criteria

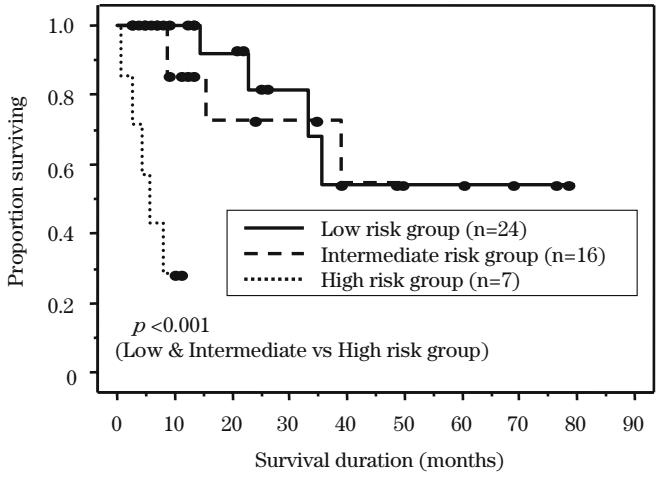

Fig. 4. Proposed risk model for survival according to combination of the two validated prognostic factors for survival. The patients in the high-risk group had a significantly shorter survival compared with survivals in the other two groups ($P < 0.001$, by log-rank test)

Discussion

While cytokine treatment has been the therapeutic mainstay for metastatic RCC for more than a decade, it has led to only modest success.[20] Although 5-FU has been used to enhance the limited efficacy of cytokine treatment, one prospective randomized trial concerning the additive efficacy of fluorouracil failed to show a benefit from the addition of 5-FU to combined IFN-α and IL-2 treatment.[21] Nevertheless, the highest response rates in metastatic RCC have been reported with a combination of IFN-α, IL-2, and 5-FU, in studies by Atzpodien and colleagues (Lopez-Hanninen et al.[12]).[13,18,19] In addition, several patients with metastatic RCC were reported to have shown complete responses elicited by combined treatment with IFN-α and tegafur-uracil.[22] These clinical results prompted us to reproduce the reported results by alternating intravenous high-dose 5-FU with tegafur-uracil; which we chose because of its few side effects and easy oral administration.

The dose of IL-2 used in the current study was even lower than the low-dose schedules used in the United States and Europe. Nevertheless, a longer overall survival (median survival time, 38.8 months) was achieved compared with survivals in previous reports.[12,13,18,19] Of note, even patients with progressive disease had a durable median survival time of 33 months. These results confirmed those in a recent clinical trial of low-dose combination therapy with IL-2 and IFN-α for metastatic RCC conducted in Japan, and reported by Akaza et al.,[23] which employed the same low dose of IL-2 as that in the current study. In the study reported by Akaza et al.,[23] the overall survival rate at the maximum follow-up period of 29 months was 66.2%, but the median survival

time could not be calculated. In contrast to the response rate of 8.5% in the present study, Akaza et al.[23] achieved a better response rate, of 21.6%, which is similar to the rates in previous reports.[13,18,19] This difference between our results and the previously reported rates may be, in part, attributable to differences in patient selection. That is, in the present study, 25% of the patients had unfavorable prognostic features, i.e., the absence of a previous nephrectomy, resistance to previous IFN-α monotherapy, or both.[24] Moreover, the majority (67.4%) of the patients in the study reported by Akaza et al.[23] had lung metastases alone, in whom treatment responses were characteristically observed, while the present study included only 27.7% of the patients with lung metastases alone. Collectively, our results show that even the extremely low dose of IL-2 we used combined with IFN-α achieved a clinical effect without inferiority to the results reported in previous studies.[12,13,20,21] Our results may be supported by the rationale proposed by Buzio et al.,[10,11] that the antitumor effect of immunotherapy is maintained at a much lower dose of IL-2 than those previously used.

The route of IL-2 administration is another important issue that affects its efficacy and toxicity. According to the systematic review reported by Baaten et al.,[25] subcutaneous administration seemed to be the preferred route for IL-2 in the combined treatment setting. Unfortunately, we lack data that could explain the difference in toxicity and efficacy between intravenous administration and the subcutaneous administration of the very low dose of IL-2 used in this study. However, in a phase II clinical trial in which a dose of IL-2 similar to the dose used in the present study was administered intravenously, adverse effects appeared to be more common than those reported for subcutaneous administration.[14] Therefore, we favored subcutaneous IL-2 administration rather than using the intravenous route, even though the former has not been approved by the health insurance system of the Japanese government.

Because only a minority of patients have had therapeutic benefits from cytokine treatment, determining the factors predictive of treatment outcome would be helpful for selecting patients suitable for cytokine treatment and enhancing the treatment benefit. Prognostic factors and a predictive algorithm for survival in patients with metastatic RCC receiving cytokine treatment have been reported by numerous investigators.[12,26–33] The median survival times, according to the proposed risk-group stratifications that were established by different parameters analyzed in each study, were: 19.9 to 47 months for the low-risk group, 9.9 to 19 months for the intermediate-risk group, and 3.9 to 8 months for the high-risk group. We employed the representative clinical factors used in those studies in the present study to predict the clinical outcome after immunochemotherapy. The well-known and widely reported risk factors – the absence of previous nephrectomy, performance status, metastasis at initial diagnosis, and hemoglobin and C-reactive protein levels – were strongly related to disease progression, overall survival, or both. The risk model in our present study, defining only two parameters, previous nephrectomy and hemoglobin level, as independent risk factors for survival, clearly discriminated the high-risk patients from the others. In accordance with previous reports, low-risk patients in our study had a favorable prognosis and high-risk patients could expect a limited survival time, indicated by the range of median survival times for each patient group. Notably, there seemed to be a potential survival benefit for intermediate-risk patients as well as low-risk patients in the current study. The median survival of more than 30 months in the intermediate-risk patients in the current study – equal to the survival of the low-risk patients – is definitely longer than previously reported. Thus, patients with intermediate-risk and low-risk features may be more likely than those with high-risk features to benefit from the treatment we used. Moreover, considering the poor prognosis of untreated patients with metastatic RCC, with a 5-year survival rate of less than 10% and a median overall survival of no more than 10 months,[34] the durable median survival observed consistently in the low- and intermediate-risk patients in the current study suggests that immunochemotherapy consisting of very low-dose IL-2, IFN-α, and tegafur-uracil may contribute to prolonged survival for patients in these groups. In contrast, for patients with high-risk features, cytokine treatment should no longer be recommended, and novel treatment strategies, such as the use of anti-vascular endothelial growth factor (VEGF)[35–37] could be considered a priority. However, given the multiple autocrine and paracrine growth-factor signaling cascades in RCC and endothelial/stromal cells, it is likely that a simple monotherapy approach to anti-angiogenic therapy will have limited efficacy.[35–37] Therefore, we believe that immunotherapy will not become obsolete in patients wih RCC, because it may be considered for inevitable disease progression after novel molecular-targeted therapy as salvage therapy or in a combined setting.[38]

The present retrospective immunochemotherapy study has the limitation of a small number of patients, and so we strongly advocate the use of randomized trials in a larger cohort of patients to prove any hypothetical survival advantage for patients receiving this therapy. In addition, augmented benefits from the addition of tegafur-uracil will require evaluation in prospective randomized trials.

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