# Original Article

## IMMUNOCHEMOTHERAPY WITH INTERFERON-$\alpha$, INTERLEUKIN-2, 5-FLUOROURACIL, AND CIMETIDINE FOR PATIENTS WITH ADVANCED RENAL CELL CARCINOMA

MAKITO MIYAKE, KIYOHIDE FUJIMOTO,
MASAHIRO TANAKA and YOSHIHIKO HIRAO
*Department of Urology, Nara Medical University*

HIROTSUGU UEMURA
*Department of Urology, Kinki University School of Medicine*

TAKESHI OTANI
*Department of Urology, Matsuzaka Central Hospital*

MASAHITO YOSHII
*Department of Urology, Saiseikai Chuwa Hospital*
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*Abstract* : Introduction. We prospectively evaluated the efficacy and safety of immunochemotherapy using INF-$\alpha$, IL-2, 5-fluorouracil (5-FU), and cimetidine in patients with metastatic renal cell carcinoma (RCC). Patients and Methods. Twenty-two patients with metastatic RCC were given 4 weeks of initial therapy consisting of IFN-$\alpha$ (3-6x$10^6$ IU/day 3 times/week), IL-2 (0.7-1.4x$10^6$ JRU/day for 5 consecutive days/week), 5-FU (150 mg/m2/day for 5 consecutive days/week), and cimetidine (800 mg/day), followed by maintenance therapy with IFN-$\alpha$, IL-2, and cimetidine. The response rate, overall and progression-free survivals, and adverse events were analyzed. Results. The median periods of therapy and follow-up were 4.4 months (range: 0.4-33) and 28.8 months (range: 1-65), respectively. The early anti-tumor effect was a complete response in one (4.5%), a partial response in 3 (13.6%), no change in 9 (40.9%), and progressive disease in 9 (40.9%). The 2-year progression-free and overall survival rates were 31% and 76%, respectively. The overall survival of cytokine-naïve group was higher than that of cytokine-resistant group ($p<0.032$). Adverse events of grade $\leq 3$ occurred in 5 patients, and 9 discontinued this therapy due to adverse events. Conclusion. The present regimen had a low response rate despite the high incidence of adverse events and should be limited to patients with cytokine-naïve metastatic RCC.

**Key words** : interferon-$\alpha$, interleukin-2, 5-fluorouracil, cimetidine, renal cell carcinoma

**Abbreviation List** INF-$\alpha$; interferon-alfa / IL-2; interleukin-2 / 5-FU; 5-fluorouracil / RCC; renal cell carcinoma / IU; international unit / ECOG; The Eastern Cooperative Oncology Group / PS; performance status / CTCAE; Commom Terminology Criteria for Advance Events / CR; complete response / PR; partial response / NC; no change / PD; progressive disease /

FdUMP; fluoro-deoxyuridine monophosphate / SNP; single nucleotide polymorphism

## INTRODUCTION

Cytokine therapy with interferon-$\alpha$ (IFN-$\alpha$) or interleukin-2 (IL-2) has been widely used for metastatic RCC. However, the response rate to such cytokine monotherapy is only about 15 to 20%. Although some Japanese trials revealed that a tumor response rate of about 30 to 40% was achieved by a combination therapy using IFN-$\alpha$ and cimetidine [1,2], the outcomes of such therapy were not satisfactory. Moreover, the more promising combination immunochemotherapy with IFN-$\alpha$, IL-2, and 5-fluorouracil (5-FU) reportedly has a response rate of 1.8 to 39% and achieved survival benefit for the patients with advanced RCC[3-10]. However, the doses of IL-2 and IFN-$\alpha$ used in those overseas studies were much higher than the doses approved in Japan. Administration of such doses would probably cause severe adverse reactions, and provoke high medical costs. Accordingly, continuation of high-dose therapy would be possible only in a limited population of patients in Japan.

On the other hand, various molecular targeted therapies have been recently developed, and are now available as promising first-line or second-line therapy against metastatic or cytokine-resistant RCC in Japan as well as the USA or Europe. However, the long-term benefits of molecular targeted therapy are still uncertain, and there are several problems with that novel therapy, such as a short duration of response, low complete response rate, and unusual severe adverse reactions in some patients, which should not be overlooked when considering this as breakthrough therapy.

In the present study, to elucidate the usefulness of immunochemotherapy which may be tolerable for patients with advanced RCC with metastasis on a long-term basis, we evaluated the efficacy and safety of our 4-agent combination immunochemotherapy using IFN-$\alpha$, IL-2, 5-FU and cimetidine at doses used commonly in Japan.

## PATIENTS AND METHODS

### Study design

The present study was a non-randomized open-label prospective trial to evaluate the response rate, progression-free survival, and adverse events of immunochemotherapy using 4 agents (namely, IFN-$\alpha$, IL-2, 5-FU, and cimetidine) for advanced RCC with metastasis. The protocol of this 4-agent combination immunochemotherapy consisted of an initial 4-week period that was followed by maintenance therapy. The initial therapy included Sumiferon®(IFN-$\alpha$; Dai-nippon Sumitomo Pharmaceuticals, Japan) at a dose of 3 to 6 $\times$ $10^6$ IU 3 times per week by subcutaneous injection ; Imunase®(IL-2 ; Shionogi, Japan) at a dose of 0.7 to 1.4 $\times$ $10^6$ JRU by intravenous infusion (over 2 hours) for 5 consecutive days per week, followed by withdrawal for 2 days; 5-FU®(Kyowa Hakko, Japan) at a dose of 150 mg/$m^2$/day by intravenous infusion (over 12 hours) for 5 consecutive days per week, followed by withdrawal for 2 days; and Tagamet®(cimetidine; Dai-nippon Sumitomo Pharmaceuticals, Japan) in 2 divided oral doses (total: 800 mg/day). The initial therapy was followed by maintenance therapy with three-agent immunotherapy (IFN-$\alpha$, IL-2, and cimetidine) excluding 5-FU. The study was discontinued if progression of cancer,

deterioration of the general condition, and/or serious adverse events were confirmed by diagnostic imaging, laboratory tests, and subjective symptoms, or definite clinical signs.

**Patient selection**

Patients with cytokine-naïve or cytokine-resistant advanced RCC with distant and/or nodal metastasis were enrolled in this study. The inclusion criteria were as follows: histopathological diagnosis of RCC based on extirpated specimen of the kidney, an age ranging from 20 to 75 years, an ECOG performance status (PS) of 0-2, measurable lesions (excluding bone metastasis) by imaging, a life expectancy greater than 3 months, and written informed consent. Patients with brain metastasis, autoimmune hepatitis, active malignant tumor of other organs, PS of $\geq$3, psychological disease including depression, serious cardiovascular or pulmonary disease, serious diabetes mellitus, and serious disease of other organs including the liver (serum bilirubin $\geq$1.5 mg/dl, GOT, GPT $\geq$100 U/l), kidney (serum creatinine $\geq$2.0 mg/dl), and bone marrow (a peripheral white blood cell count $<$4000/mm$^3$, platelet count $<$100.000/mm$^3$), were excluded from this study. Patients with allergies to IFN-$\alpha$, IL-2, cimetidine, any substance of bovine origin, or vaccines were excluded, too. The exclusion criteria included prior chemotherapy and radiation therapy. Prior cytokine therapy of RCC within 3 months before entry to the present study was an exclusion criteria. Concomitant use of other cytokines or biological response modifiers, other anticancer agents, and radiation therapy was prohibited.

The Institutional Review Board approved this clinical study, and all of the patients received an explanation of the study before giving us their informed consent.

**Evaluation by response criteria and survival rate**

Imaging was performed every 3 months to assess the measurable lesions and to detect any new lesions. The response rate at 3 months was determined to assess the early anti-tumor effect of this treatment. The anti-tumor effect was evaluated from the maximum response (the greatest reduction of tumor size) among all imaging findings, and the response rate was assessed in accordance with the definitions specified in the General Rule for Clinical and Pathological Studies on Renal Cell Carcinoma[11]. Toxicity and adverse events were assessed according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) to evaluate the safety of the present therapy. The overall and progression-free survivals from the start of treatment until death and progression were estimated by the Kaplan-Meier method, and the significance of differences ($p<0.05$) was assessed by the log-rank test.

## RESULTS

**Patient and tumor characteristics**

Twenty-two patients (18 men and 4 women) diagnosed as having measurable metastatic lesions of RCC were enrolled between May 2001 and April 2004 at Nara Medical University (Table 1). Their mean age was 60.8±8.6 years (range: 42 to 76 years). Fifteen patients had metastasis-associated symptoms while 7 were asymptomatic. The PS was 0 in 20 patients and PS 1 in 2.

Table 1. Patients' backgrounds (n=22)

| | | |
|---|---|---|
| Mean age (range) | | 60.8±8.6 (42-76) yrs |
| Gender | | |
| | men | 18 |
| | women | 4 |
| Performance status | | |
| | 0 | 20 |
| | 1 | 2 |
| Prior treatment | | |
| | primary lesion | |
| | nephrectomy | 21 |
| | partial nephrectomy | 1 |
| | metastatic lesion | |
| | IFN-α / IFN-α + IL-2 | 9 / 3 |
| | surgery | 2 |
| | none | 10 |
| | Metastatic sites | |
| | lymph node | 11 (alone in 3) |
| | retroperitoneal | 7 |
| | mediastinal | 2 |
| | cervical | 2 |
| | lung | 17 (alone in 6) |
| | bone | 7 |
| | liver | 2 |
| | pancreas | 2 |
| | adrenal | 1 |
| | skin | 1 |
| | bronchus | 1 |

IFN-α, interferon-α; IL-2, interleukin-2

Twenty-one patients underwent nephrectomy and one underwent partial nephrectomy prior to this therapy. In the case with lymph node enlargement, lymphadenectomy was performed simultaneously. Two patients had prior surgery for metastatic lesion: lymphadenectomy or pulmonary wedge resection. Twelve patients had already been given prior immunotherapy (9 had received IFN-$\alpha$ monotherapy while 3 had received IFN-$\alpha$ followed by IL-2), and were considered as cytokine-resistant with no efficacy noticed.

The primary RCCs were staged T1a in 2 patients, T1b in 6, T2 in 5, T3a in 3, T3b in 2, and T4 in 4, and graded G1 in 2 patients, G2 in 14, and G3 in 6. The histopathological diagnoses were 17 clear cell carcinomas and 2 granular cell carcinomas, one spindle cell carcinoma, one papillary carcinoma, and one cystic-associated renal cell carcinoma. The N categories at the time of enrollment were N0 in 14 patients, N1 in 4, and N2 in 4. Nodal metastases were identified in the cervical lymph nodes in 2, mediastinal lymph nodes in 2, and retroperitoneal lymph nodes in 7. Distant metastases were identified in the lungs in 17 patients, bone in 7, liver in 2, pancreas in 2, adrenal gland in one, bronchus in one, and skin

Table 2. Adverse events in combination therapy of IFN- $\alpha$, IL-2, 5-FU, and cimetidine

| | Grade (CTCAE v3.0) | | | | | No.patients (%) |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| *Full-like symptom* | | | | | | |
| fever | 5 | 9 | 0 | 0 | 0 | 14(64) |
| fatigue (malaise) | 6 | 1 | 0 | 0 | 0 | 7(32) |
| *Gastrointestinal* | | | | | | |
| anorexia | 9 | 3 | 1 | 0 | 0 | 13(59) |
| diarrhea | 1 | 1 | 0 | 0 | 0 | 2(9) |
| stomach ulcer | 0 | 0 | 0 | 1 | 0 | 1(4.5) |
| *Hepatic* | | | | | | |
| AST, ALT | 2 | 2 | 0 | 0 | 0 | 4(18) |
| *Cardiovascular* | | | | | | |
| cardiac ischemia | 0 | 0 | 1 | 0 | 0 | 1(4.5) |
| *Renal* | | | | | | |
| creatinine | 3 | 1 | 0 | 0 | 0 | 4(18) |
| *Neurophsycological* | | | | | | |
| depression | 2 | 0 | 0 | 0 | 1* | 3(14) |
| *Hematologic* | | | | | | |
| leukocytopenia | 2 | 0 | 0 | 0 | 0 | 2(9) |
| hemoglobin | 0 | 0 | 1 | 0 | 0 | 1(4.5) |
| *Skin* | | | | | | |
| rash | 1 | 0 | 0 | 0 | 0 | 1(4.5) |
| alopecia | 1 | 0 | 0 | 0 | 0 | 1(4.5) |

* suicide case

in one. Nine patients had metastasis confined to a single organ (lung in 6 and lymph node in 3), while the remaining 14 patients had metastases in multiple organs.

**Adverse events and tolerance of immunochemotherapy**

For all 22 patients, the median duration of therapy was 4.4 months (mean: 8.7±9.3, range: 0.4 to 33 months), and the median follow-up period was 28.8 months (mean: 26.4±19.8, range: 1 to 65 months). Nineteen (86%) completed their initial therapy, while 3 patients discontinued it due to duodenal ulcer, fever with anorexia and malaise, and impaired renal function. Of 19 patients who completed the initial therapy, 6 patients discontinued the maintenance therapy within 3 months due to adverse events (malaise, anorexia, respiratory distress, suicide, and impaired liver or renal function), while 13 patients (68%) proceeded to and continued the maintenance therapy for more than 3 months. The most frequently observed adverse event was fever (64%), followed by anorexia (59%), and fatigue or malaise (32%) as shown in Table 2. Although these events had a high incidence, one patient only had anorexia of grade 3. Elevation of the hepatic transaminases and an increase of creatinine occurred in 18% and 18%, respectively, and those adverse events were grade 1 or 2. Adverse events of grade 3 or more by the CTCAE v3.0 were observed in 5 patients, one of whom developed depression and committed suicide. Diarrhea and leukocytopenia occurred in 9%, but never led to discontinuation.

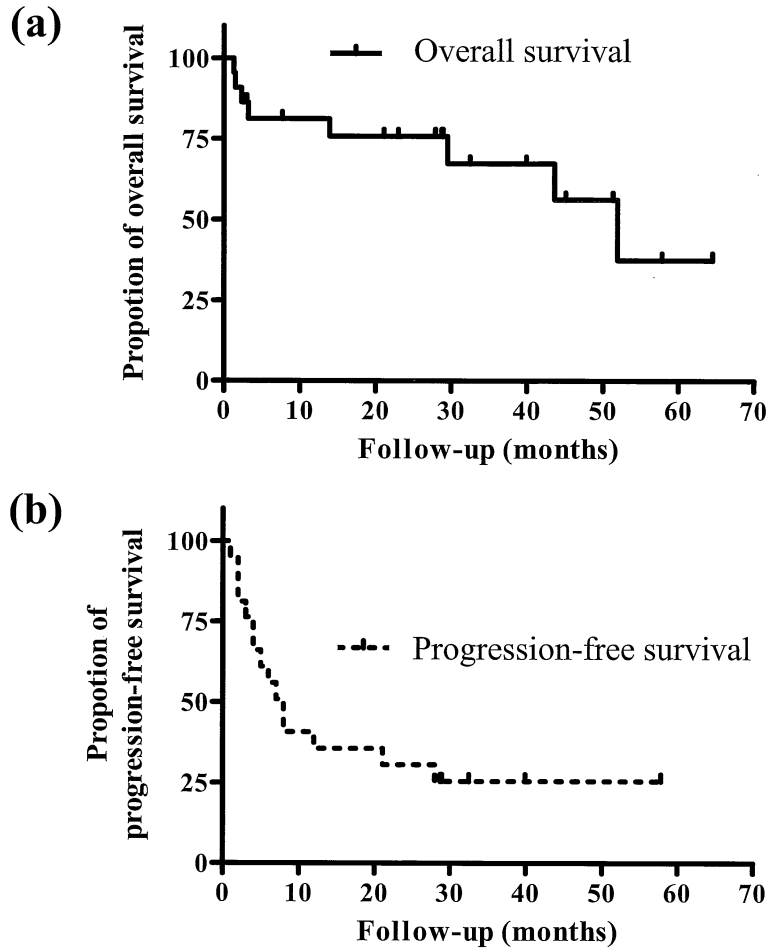


Fig. 1. The Overall survival (a) and progression-free survival (b) curves in patients with advanced metastatic renal cell carcinoma treated with a combination immunochemotherapy of IFN-$\alpha$, IL-2, 5-FU and cimetidine.

**Early anti-tumor effects and survival rates**

One patient achieved a complete response (CR: 4.5%), 3 had a partial response (PR: 13.6%), 9 showed no change (NC: 40.9%), and 9 had progressive disease (PD: 40.9%) at 3 months. The response rate to this therapy was 18.2%. All 4 responders had lung metastasis; the CR patient had metastasis only in the lung, while the PR patients had metastasis in other organs. One and 5 patients of cytokine-resistant group showed PR and NC, respectively, while one, 2, and 4 patients of cytokine-naïve group showed CR, PR, and NC, respectively. The CR patient is still alive after 29 months and is disease-free without any additional treatment. Two and 5 patients showed disease progression during the initial therapy and maintenance therapy, respectively, and all of them discontinued their therapy due to

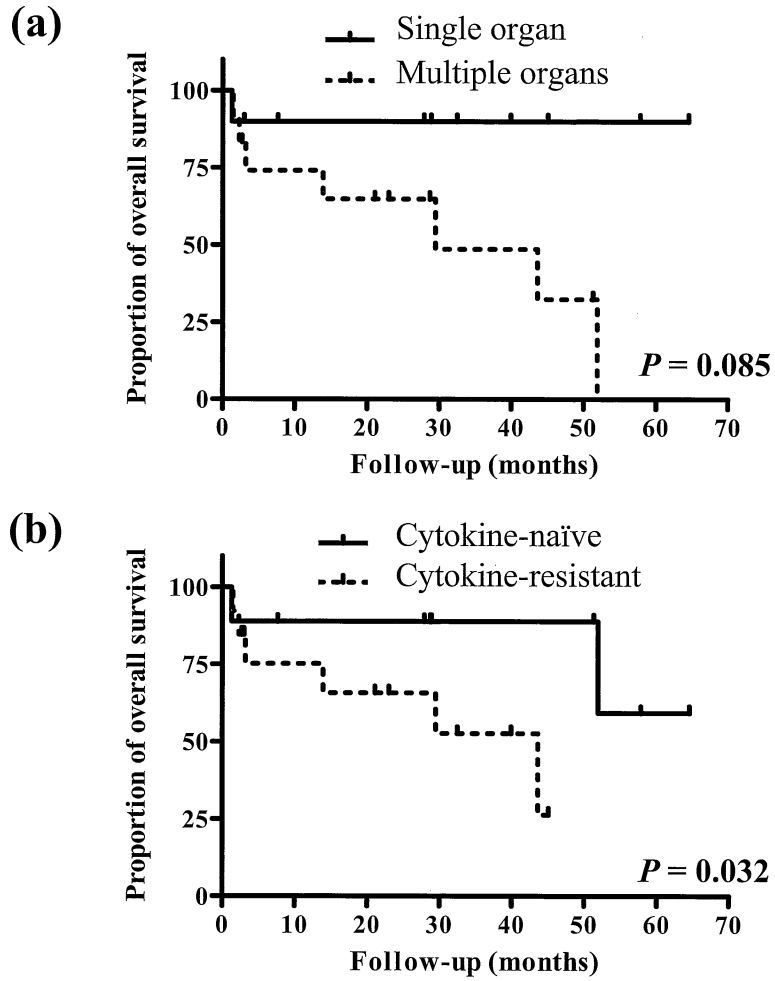


Fig. 2. (a) Comparison of the overall survival after combination therapy of IFN-$\alpha$, IL-2, 5-FU and cimetidine between patients with metastasis in a single organ and multiple organs showing no statistical differences (p=0.085); (b) Comparison of the overall survival after the present combination immunochemotherapy between patients with cytokine-naïve and cytokine-resistant metastatic RCC showing statistical differences (p=0.032)

aggressive disease progression. The 1-year, 2-year, and 5-year progression-free survival rates for all 22 patients were 36%, 31%, and 25%, respectively, and the 1-year, 2-year, and 5-year overall survival rates for all 22 patients were 82%, 76%, and 39%, respectively (Fig. 1).

In the subgroup analysis of all 22 patients, comparison of overall survivals between groups with single-organ metastasis and multiple-organ metastasis showed no significant difference (p=0.085, Fig. 2a). The overall survival of cytokine-naïve group was higher than that of cytokine-resistant group (p=0.032 Fig. 2b). There were no differences in the overall survivals among the tumor grades or the metastasis lesions.

## DISCUSSION

The use of various anticancer drugs, such as mitomycin[12], vinblastine[13], and 5-FU, in combination with cytokines for the treatment of advanced RCC has been investigated. According to Wirth[13], treatment with IFN-$\alpha$ plus vinblastine achieved CR in 2% and PR in 25%; i.e., the improvement was not much better than cytokine monotherapy. Wadler et al.[14] focused on the synergistic effect of interferons and anti-cancer agents, and achieved response rates as high as 63% with a combination of IFN-$\alpha$ and 5-FU in the treatment of advanced colorectal carcinoma. 5-FU is converted by thymidine kinase into fluoro-deoxyuridine monophosphate (FdUMP), which inhibits the target enzyme thymidine synthase. Interferons exert a synergetic effect by promoting the formation of FdUMP. Elias et al.[15] reported that colorectal cancer cell proliferation was strongly inhibited when 5-FU was administered after interferon treatment, and suggested that interferon inhibited the drug-resistance mechanisms of the tumor cells.

Variation of response to combination therapy using IL-2, IFN-$\alpha$, and 5FU may be attributed to the differences in the backgrounds of the patients who are given various doses, at different times and routes[3-10]. Above all, the dose of IL-2 seems to have a great influence on the response rate. However, it is difficult to use IL-2 at the doses employed in the early studies because IL-2 is associated with serious adverse reactions that occur in a dose-dependent manner, and the approved dose in Japan is relatively low. Negrier et al.[5] conducted a randomized controlled study and divided the patients into 2 groups given IFN-$\alpha$ and IL-2 combined with and without 5-FU. They achieved response rates of 8.2% and 1.4%, respectively, but there was no significant difference in the long-term survival between the groups. Atzpodien et al. compared a group of patients treated with 3-agent combination therapy (IFN-$\alpha$, IL-2, and 5-FU) and other groups of patients treated with tamoxifen or IFN-$\alpha$ plus vinblastine[3, 8]. They reported that this 3-agent regimen was superior in terms of the response rate and survival prognosis. However, the efficacy of such 3-agent therapy varied between studies, and it has not become a standard regimen for the treatment of advanced RCC yet.

Cimetidine has anti-tumor effects, such as stimulation of lymphocyte activity and inhibition of tumor growth-promoting effect of histamine, in various malignant tumors[16]. According to Marshall et al.[17], a response rate of 33.1% including CR of 7% was achieved by using a combination of cimetidine and coumarin, while Inhorn et al.[18] reported that cimetidine monotherapy at a high-dose of 2,400 mg/day achieved CR in 2 of 38 patients. Kotake and Kinouchi et al.[1,2] reported a response rate of 30 to 40% with combination therapy using IFN-$\alpha$ plus cimetidine (800 mg/day) and survival benefits in the responders in their early reports. However, Kinouchi et al.[19] have recently reported that there was no significant difference in the response rate (13.9% vs. 2.86%) or progression-free survival in a prospective randomized trial between the combination therapy of IFN-$\alpha$ plus cimetidine and IFN-$\alpha$ monotherapy.

In the present regimen, the response rate was 18.2%, and the non-progression rate was 59.1% including NC of 40.9%. These results seemed to show no additional effects of the combination therapy on the response rates of cytokine monotherapy reported previously. In

the subgroup analysis, it was reported that a low-dose combination therapy of IL-2 and IFN-$\alpha$ showed a relatively favorable response rate of 38.7% in patients only with lung metastasis[20]. In our series, the number or site of metastasis showed no influence on the overall survivals, but cytokine-naïve group showed a significantly superior overall survival when compared to cytokine-resistant group. Thus, the present combination therapy might give survival benefits somewhat to cytokine-resistant metastatic disease. However, we could not draw concrete conclusions from our present results because our series was small and the analysis period was short.

Recently, molecular-targeting agents have been developed and introduced into clinical practice. However, their optimal indications and true long-term outcomes have not been determined yet. On the other hand, genetic polymorphisms of signal transducer and activator 3 were assessed among patients with metastatic RCC and considered as a useful predictive marker of the response to IFN-$\alpha$[21]. Similarly, a single nucleotide polymorphism (SNP) in the promoter region of thymidylate synthase gene or SNP related to dihydropyrimidine dehydrogenase activation reportedly showed an association with the prognosis of colorectal cancer or the response to 5-FU[22,23]. Information obtained through such SNP analysis will be useful in the selection of therapies that are tailored for the individual patient. Thus, the role of the conventional cytokine therapy in advanced RCC may change in the near future, and local treatment of metastatic foci by surgical resection or stereotactic radiosurgery and systemic treatment by using immunotherapy, chemotherapy, or molecular targeted therapy, will eventually be combined to provide true multidisciplinary treatment.

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