Introduction

Renal cell carcinoma is resistant to chemotherapy and radiotherapy and its prognosis is poor in patients with metastasis. The disease is mainly treated with surgery or immune therapy using interferon (IFN) or interleukin 2 (IL-2). IFN consists of a group of antiviral proteins secreted from cells of vertebrates in response to various inducing agents. It inhibits cell growth and modulates immune responses. IFN has been used alone or in combination with
Although the response rate of IFN depends on its type, target groups, and therapeutic regimens, it is generally considered to range from 12 to 19% based on the results from a population of more than 1,000 patients (Table 1). 3,4)

1. Dosage and administration method

IFN is known to stimulate immunity by increasing NK activity, enhancing the expression of MHC class I antigen, and increasing the activities of macrophages and K cells. However, it has not been determined whether the effect of IFN on renal cell carcinoma results from such immunoactivating effects or its inhibitory effect on cell growth.

Quesada1) and Marushige et al.2) reported that IFN therapy for advanced renal cell carcinoma produced a response rate of 36.5% and 16.7%, respectively. Since then, IFN therapy has been examined in many clinical studies as the mainstream treatment for renal cell carcinoma. Natural-type interferon (nIFN), such as Sumiferon® (lymphoblastoid-IFN) and OIF® (leukocyte-IFN), and recombinant interferon (rIFN), such as Canferon® (IFN-α2a) and Intron A® (IFN-α2b), are generally used in Japan.

Although the response rate of IFN depends on its type, target groups, and therapeutic regimens, it is generally considered to range from 12 to 19% based on the results from a population of more than 1,000 patients (Table 1).3,4)

### Table 1  IFN Therapy for Renal Cancer

| IFN                          | Number of institutions | Number of patients | Response rate (%)
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>A. Efficacy rate by the type of IFN</strong></td>
<td></td>
<td></td>
<td>CR</td>
</tr>
<tr>
<td>IFN-α</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>natural leukocytes</td>
<td>6</td>
<td>141</td>
<td>6</td>
</tr>
<tr>
<td>natural lymphoblastoid</td>
<td>11</td>
<td>398</td>
<td>4</td>
</tr>
<tr>
<td>recombinant</td>
<td>16</td>
<td>573</td>
<td>10</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>6</td>
<td>121</td>
<td>1</td>
</tr>
<tr>
<td><strong>B. Titer and efficacy rate of IFN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily dose (MU)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>6</td>
<td>97</td>
<td>6</td>
</tr>
<tr>
<td>5–10</td>
<td>3</td>
<td>208</td>
<td>13</td>
</tr>
<tr>
<td>10–20</td>
<td>5</td>
<td>131</td>
<td>19</td>
</tr>
<tr>
<td>&gt;20</td>
<td>9</td>
<td>332</td>
<td>12</td>
</tr>
</tbody>
</table>

CR: complete response, PR: partial response

(Table 1 modified)

(Wirth, M.P.: Urol Clin North Am 19933) modified)
the initial 3 months of treatment, the administration of IFN is discontinued at 3 months in patients in whom the disease progresses in spite of IFN therapy.

2. Indications of IFN therapy and prognostic factors

A recently published prospective randomized comparative study showed that IFN-α prolonged the survival period: 167 patients with advanced renal cell carcinoma treated with IFN (10 MU, thrice weekly for 12 weeks) showed an increase in median survival period by 2.5 months as compared with 168 control patients treated with medroxyprogesterone hydrochloride (300 mg/day for 12 weeks continuously).\(^5\) Another study showed an increase in the survival period by about 30 weeks in patients treated with vinblastine (VBL) + IFN as compared with those treated only with VBL.\(^6\) However, there is a report that IFN did not prolong survival as compared with progesterone.\(^7\) Thus, the effect of IFN in prolonging survival has not been established. A recent study reported that IFN as used for the adjuvant therapy after radical nephrectomy had no effect on the survival period or prevention of recurrence.\(^8\)

Previous clinical findings indicate that beneficial effects from IFN therapy can be expected in patients to whom any of the following factors apply: (1) pulmonary or lymph node metastasis, (2) removal of the primary lesion, (3) good performance status (PS), (4) no marked increase in CRP, ESR, or IAP, (5) no spindle cell cancer component, and (6) a long interval from nephrectomy to recurrence.\(^8\)

3. Adverse reactions

Most patients treated with IFN complain of influenza-like symptoms (fever, chill, myalgia, and malaise). Other adverse reactions that may often occur include headaches, anorexia, leukopenia, thrombocytopenia, and hepatopathy. However, all these adverse reactions are resolved by withdrawing IFN. Attention should be paid to rare adverse reactions, such as depression symptoms, interstitial hepatitis, transient visual loss, and epileptic seizure.\(^4,5,10\) Combination with Sho-saiko-to is contraindicated because it may induce interstitial pneumonia.

Gene Recombinant IFN-γ

Imunomax® (IFN-γ1a) is used as a gene recombinant IFN-γ in Japan.

1. Administration method and therapeutic results

In general, gene recombinant IFN-γ is administered by intravenous drip infusion at 2 to 3 MJRU/m² every day, or at 10 MJRU/m² once daily for 5 days consecutively, which is repeated twice with a withdrawal interval of 9 days. As with IFN-α, the gene recombinant IFN-γ produced variable response rates among medical institutions. A recent report shows a response rate of 10% achieved by once-weekly subcutaneous injection of 2 MJR.\(^11\) A Canadian group reported a response rate of 4.4% in 181 patients with advanced renal cell carcinoma treated with IFN-γ1b once weekly.\(^12\) Horoszewicz et al.\(^2\) reported that IFN-γ was effective in 11 of 121 patients (9%) when administered every day or 5 days a week. Previous reports show slightly higher response rates with IFN-α. (Table 1)
2. Adverse reactions
Recombinant IFN-γ causes almost the same adverse reactions as IFN-α, such as fever, leukopenia, thrombocytopenia, depression, and interstitial pneumonia.

Combination of Different Types of IFN or Combination of IFN and Other Drugs
Various combinations including IFN-α have been attempted to improve therapeutic effectiveness.

1. Combination with IFN-γ
IFN-α was combined with IFN-γ to obtain a possible synergistic effect. This was plausible because they bind with different receptors and because IFN-α induces the expression of class I, while IFN-γ induces the expression of Class II. However, the combination failed to provide a higher therapeutic effect than IFN-α alone.3,13)

2. Combination with retinoic acid
Retinoic acid, which is an active principle of vitamin A, inhibits the proliferation of renal cell carcinoma and increases the antitumor effect of IFN. Motzer et al.14) reported a response rate as high as 30% from this combination. However, recent reports from two medical institutions described a response rate of 4% and 14%,15) indicating the absence of a combination effect.

3. Combination with IL-2
In a randomized comparative study in which patients were treated with IFN-α alone (18MU), IL-2 alone (18MU/m²), or both, Negrier et al.16) reported the superiority of the combination in response and one-year survival rates. Recently, the combination of low-dose IL-2 and IFN-α with fewer adverse effects has been examined: the regimen involves the subcutaneous administration of 1.8MU of IL-2 once or twice weekly and intramuscular injection of 1.8MU of IFN-α for 4 weeks; this comprises one course and is repeated every 3 months. Using the regimen, Buzio et al.17) reported a response rate of 12% and a 3-year survival expectancy of 47% in 50 patients. However, Clark et al.18) who subcutaneously administered the same dose of IL-2 and 8MU of IFN-α every day reported a response rate of as low as 5.3% and one-year survival rate of 16%. The upper limit of IL-2 covered by the Japanese medical insurance is 2.1 MU. Long-term results from the combination therapy with low-dose IL-2 and IFN are expected.

4. Combination with chemotherapy
The combination with VBL or 5-fluorouracil (5-FU) has been attempted because VBL is the only chemotherapy agent that provided a response rate of about 10% and because 5-FU increased its in vitro cytotoxic effect with the addition of IFN-α.

(1) Combination with VBL
This combination has been attempted since around 1985, and has been reported to provide a response rate ranging from 10 to 35%. However, a randomized comparative study comparing IFN alone and combination of IFN and VBL in 3 medical institutions showed no difference in clinical effectiveness, indicating no combination merit19,20) (Table 2). However, it should be noted that a study reported that a response rate of 15% could be obtained from the combination even in patients who did not respond to IL-2.21)

(2) Combination with 5-FU
A Japanese multi-center joint study by a research group on renal cancer showed a response rate of 20% (including 3 CR cases) in 53 patients treated with 3MU of IFN-α and 600mg/m² of 5-FU for 12 weeks22) (Table 2). However, the result does not surpass results previously obtained with IFN-α alone. Although a combination of IFN-α, 5-FU, and IL-2 has recently attracted attention (Table 3), it produced variable response rates ranging from 2 to 39% among institutions, and the addition of 5-FU tended to increase adverse reactions
Table 2 Combination with IFN-α and Chemotherapy Agents

<table>
<thead>
<tr>
<th>Reporter (year)</th>
<th>IFN-α</th>
<th>Drug</th>
<th>Number of patients/efficacy rate (%)</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarna, G. (1987)</td>
<td>3 MU/5x/w/12wks/im(1)</td>
<td>0.1 mg/kg/w (---)</td>
<td>22/14</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Fossa, S.D. (1992)</td>
<td>18 MU/3x/w/im</td>
<td>0.1 mg/kg/w/ever3wks (---)</td>
<td>66/24</td>
<td>5-year survival rate: 9%</td>
</tr>
<tr>
<td>Paolorossi, F. (1995)</td>
<td>3 MU/3x/w/sc</td>
<td>0.1 mg/kg/w/ever3wks</td>
<td>13/15</td>
<td>5-year survival rate: 9% (Past history with IL-2 therapy)</td>
</tr>
<tr>
<td>Tsavaris, N. (2000)</td>
<td>5 MU/3x/w/sc</td>
<td>6 mg/m²/w/ever2wks (---)</td>
<td>50/18</td>
<td>No significant difference, response period: 23 mos</td>
</tr>
<tr>
<td>[5Fu] continuous iv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elias, L. (1996)</td>
<td>5 MU/m²/1, 3, 5d/w/sc (2)</td>
<td>750 mg/m²/1, 3, 5d/w/ever3wks</td>
<td>40/13</td>
<td>No CR</td>
</tr>
<tr>
<td>Igarashi, T. (1999)</td>
<td>3 MU/m²/3x/w/12wks</td>
<td>600 mg/m²/1x/5d→1x/w/3~12wks</td>
<td>53/20</td>
<td></td>
</tr>
<tr>
<td>Murphy, B.R. (1992)</td>
<td>9 MU/3x/w</td>
<td>750 mg/m²/1~5d/w→1x/w</td>
<td>14/0</td>
<td>Not effective</td>
</tr>
<tr>
<td>Haarstad, H. (1994)</td>
<td>12 MU/3x/w</td>
<td>600 mg/m²/1x/1~5d/3 &amp; 4w (3)</td>
<td>31/23</td>
<td></td>
</tr>
</tbody>
</table>

Response: CR + PR, iv: intravenous, im: intramuscular, sc: subcutaneous, d: day, w: week, wks: weeks, mos: months, →: subsequently
(1): Intramuscular injection of 3M units, 5 days per week for 12 weeks
(2): Subcutaneous injection of 5M units/m², 1, 3 and 5 days a week
(3): Three different regimens are available.

Table 3 Combination Therapy of IFN-α, IL-2, and 5-FU

<table>
<thead>
<tr>
<th>Reporter (year)</th>
<th>IFN-α</th>
<th>IL-2</th>
<th>5Fu</th>
<th>Number of patients/response rate (%)</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ravaud, A. (1998)</td>
<td>6 MU/1x/d/1, 3, 5 d/w</td>
<td>9 MU/d/1~6 d/8wks sc</td>
<td>600 mg/m²/1~5d/w/1x/w/4w/iv bolus</td>
<td>111/2</td>
<td></td>
</tr>
<tr>
<td>van Herpen, C.M. (2000)</td>
<td>6 MU/m²/sc (1)</td>
<td>20 MU/m²/3x/w/1, 4w sc</td>
<td>750 mg/m²/1x/w/5~8w</td>
<td>51/12 (total of 2 groups)</td>
<td>No CR Grade 3/4 toxicity: 55.8%</td>
</tr>
<tr>
<td>Olencik, D. (2001)</td>
<td>5 MU/m²/1, 3, 5d/w/4wks</td>
<td>5 MU/m²/1~5w/4wks sc</td>
<td>300 mg/m²/5x/w/1w</td>
<td>25/28</td>
<td></td>
</tr>
<tr>
<td>Atzpodien, J. (2001)</td>
<td>5 MU/m²/2</td>
<td>10 MU/m²/3</td>
<td>1,000 mg/m²/1x/d/1/5~8w</td>
<td>51/39</td>
<td>CR(7) survival: 24mos</td>
</tr>
</tbody>
</table>

(1) 1x/w/1, 4w & 3x/w/2, 3w: Once weekly in Weeks 1 and 4 and thrice weekly in Weeks 2 and 3
(2) 1x/1d/1&4w, 1x/1, 3d/2 & 3w (increased to 10MU/m²/1, 3, 5 d/5 to 8w
(3) 2x/d/3 to 5d/1 & 4w* 5x10MU/m²/1, 3, 5d/w/2 & 3 w*: twice daily from Days 3 to 5 in Weeks 1 and 4
such as anorexia, fever, malaise, and leukopenia.\textsuperscript{23,24}) However, since it is expected to improve the response rate and prolong the response period by IL-2, it is necessary to accumulate more clinical results to identify the optimum dose of IL-2 and confirm whether the combination has a long-term tumor reducing effect or not.

**Conclusions**

Although IFN therapy has provided a response rate of only 10 to 20\% in the treatment of advanced renal cell carcinoma, it is expected to prolong survival in patients who respond to it. Combinations with other drugs have been attempted to increase its therapeutic effect. It will be particularly necessary to examine the long-term results of regimens including IL-2.

**REFERENCES**

17) Buzio, C., Andrulli, S., Santi, R. et al.: Long-term immunotherapy with low-dose interleukin-2 and interferon-alpha in the treatment of...
patients with advanced renal cell carcinoma. 
*Cancer* 2001; 92: 2286–2296.


