Repeated regression of pulmonary metastases from renal cell carcinoma after treatment using different interferon-alpha preparations

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ABSTRACT
A 49-year-old man with pulmonary metastasis from renal cell carcinoma (RCC) was treated with recombinant IFN-α2b (Intron A®). A complete response was achieved within 4 months and thereafter persisted for 5 years until he developed another lung lesion. Interleukin-2 (Imunace®) was administered without any response. Finally, he was treated by natural IFN-α (OIF®). The pulmonary lesion achieved a partial response after 11 months of treatment. Because IFN-α preparations include different subtypes, changing the use of IFN-α preparations may thus be a potentially useful option for the successful immunotherapy of RCC.

Metastatic renal cell carcinoma (RCC) is resistant to conventional chemotherapy and radiotherapy. A wide variety of immunotherapy protocols using interferon-alpha (IFN-α) and/or interleukin-2 (IL-2) have been developed, however, the response rate remains unsatisfactory at around 10–20% (2, 7). IFN-α represents a large family of structurally related genes consisting of at least 14 subtypes (3). Each subtype may have different biological activities. We herein report a case of RCC whose pulmonary metastasis initially responded positively to recombinant IFN-α2b, and a good response was again seen using natural IFN-α preparations.

A 49-year-old man presented with gross hematuria and left flank pain in September 1996. Abdominal computerized tomography (CT) revealed a left renal mass measuring 8.8 cm in size. A chest X-ray demonstrated a pulmonary metastatic lesion (Fig. 1A). The patient underwent a left radical nephrectomy. Based on the pathological findings, it was diagnosed to be clear cell type RCC with a nuclear grade of 2 > 3. The tumor extended into the perinephric fat, with negative margins of resection and no nodal involvement. He was treated with 6.0 × 10^6 I.U. recombinant IFN-α2b (Intron A®, Schering-Plough Pharmaceuticals Co. Ltd., Osaka, Japan) × 3/week. A complete regression was thus achieved after 4 month (Fig. 1B). This immunotherapy continued for 4 years with appropriate dose reductions. In September 2002, a new lesion of pulmonary metastasis was found by CT (Fig. 2A). IL-2 (Imunace®, Shionogi Pharmaceuticals Co. Ltd., Osaka, Japan) was administered at 1.4 × 10^6 I.U. × 5/week for 2 months without any response. Therafter, he was treated by 5.0 × 10^6 I.U. natural IFN-α (OIF®, Otsuka Pharmaceuticals Co. Ltd., Tokyo, Japan) × 2/week. The pulmonary lesion demonstrated a partial response after 11 months of treatment (Fig. 2B). The patient’s disease is no longer progressing and he is in a healthy condition, although 8 years have passed since the initial diagnosis of metastatic RCC.

Immunotherapy is a widely accepted standard therapy for metastatic RCC. However, its efficacy remains insufficient at around 10–20% (2, 7). IFN-α is frequently chosen as the standard treatment for initially diagnosed RCC with metastases. When the patient turns out to be resistant to IFN-α, the immunotherapy regimen is sometimes switched to IL-2. Indeed, some patients resistant to IFN-α have been
reported to respond to IL-2 with a good prognosis (8). Immunotherapeutic agents including IFN-α and IL-2 may have different antitumor activities even in the same patient. Because IFN-α preparations include different subtypes, the use of IFN-α preparations of different origins can also be a potentially useful therapeutic option for the treatment of RCC. Moreover, there are some differences between recombinant and natural IFN-α2, especially, regarding modification of glycosylation in the mature form of native IFN-α2b (Table 1) (11). Horiguchi and Uchida reported a case of metastatic RCC which responded to natural IFN-α (OIF®) even though the patient did not respond to any other type of natural IFN-α (Sumiferon®) (5). This case suggests that differences in the subtypes contained in IFN-α preparations may cause different biological and antitumor activities.

Table 1  Characterizations of the two types of IFN-α preparations

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<thead>
<tr>
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<th>Intron A</th>
<th>OIF</th>
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<tbody>
<tr>
<td>type</td>
<td>recombinant</td>
<td>native</td>
</tr>
<tr>
<td>subtype</td>
<td>2</td>
<td>2/8</td>
</tr>
<tr>
<td>Sugar chain (IFN-α2)*</td>
<td>−</td>
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* Naturally occurring IFN-α2 is modified by the glycosylation of the mature form of native IFN-α2 in the human body.
activities on RCC.

The present report seems to be the first case of RCC which responded to recombinant IFN-α and natural IFN-α asynchronously. Natural IFN-α preparations include several subtypes of IFN-α with different biological activities. When Yanai et al. characterized the anti-tumor activities of various IFN-α subtypes on RCC cell lines in vitro (10), IFN-α8 most potently inhibited cell proliferation as well as upregulated the expression of the HLA class I antigen. Indeed, OIF® includes the IFN-α8 subtype (9). Therefore, IFN-α8 may have exerted an antitumor effect that was not induced by IFN-α2. Ariyasu et al. reported that IFN-α8 effectively augments in vitro Th1-type immunity in the peripheral blood mononuclear cells of hepatitis B virus (HBV)- and hepatitis C virus (HCV)-infected patients (1, 4). It is also well known that the production of IFN-α subtypes is regulated by different interferon regulatory factors (6). Both our findings and those of Horiguchi and Uchida (5) showed differences in the biological activities of the subtypes of IFN-α in a clinical setting. To date there is no means to predict the outcome of immunotherapy. Some patients respond to IFN-α, but not to IL-2, while others respond IL-2 but not IFN-α. Individual-based immunotherapy should thus be carefully taken into consideration. Because IFN-α preparations include different subtypes even among natural type IFN-α preparations, changing the use of IFN-α preparations may thus be a potentially useful option for the successful immunotherapy of RCC.

REFERENCES