

COMPLETE RESOLUTION OF MULTIPLE PULMONARY METASTASES OF RENAL CELL CARCINOMA FOLLOWING INTRAVENOUS DRIP INFUSION OF r-INTERLEUKIN 2: A CASE REPORT

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A 68-year-old man with multiple pulmonary metastases from a right renal cell carcinoma was treated with alpha interferon, but there was no improvement. For this reason, alpha interferon was ceased, and daily monotherapy with recombinant interleukin-2 (1,000,000 units/day) was commenced. After 4 months, plain chest x-ray and chest CT revealed complete clearance of the pulmonary metastases. There were no side effects except general fatigue and slight fever. Immunological studies revealed elevation of the leukocyte count (lymphocytes, eosinophils) and enhancement natural killer activity. At 10 months after discontinuation of the drug, recurrence has not been observed. Our case indicates the potential value of interleukin-2 following treatment with alpha interferon.

Key words: r-Interleukin 2, Renal cell carcinoma, Pulmonary metastasis

INTRODUCTION

Renal cell carcinoma, which is often resistant to radiotherapy and chemotherapy, and against which hormone therapy is effective in no more than 5% of the cases, is generally considered very difficult to treat. Ever since Quesadel et al.¹⁾ utilized human leukocyte interferon to treat renal cell carcinoma in 1983 and reported its effectiveness, various types of alpha interferon have been used, but the efficacy rate has never been greater than about 20%²⁻⁵⁾. Interleukin 2 is a lymphokine discovered by Morgan⁶⁾ in 1986 as a T-cell growth factor, and it plays an important role in modulating the immune system. Recombinant interleukin 2 (r-IL-2) is now available and we can take advantage of the natural killer (NK) and lymphokine-activated killer (LAK)-inducing and activating actions of r-IL-2 in the treatment of malignant tumors. We report a patient in whom multiple pulmonary metastases of a renal cell carcinoma resistant to alpha interferon, but which completely disappeared following intravenous infusion of r-IL-2.

CASE REPORT

A 68-year-old man was admitted to our hospital with dysuria on November 11, 1986. He had undergone laminectomy of the 5th cervical vertebra for sclerosis of the posterior longitudinal ligament of the neck on November 10, 1981. Neurogenic bladder had developed secondarily to the above-mentioned procedure. The patient's urination was being monitored, and when IVP and CT were performed in January, 1987, for microscopic hematuria, a tumor of the right kidney was discovered and the patient was hospitalized.

On February 23, 1987, a transperitoneal radical right nephrectomy was performed. The resected kidney measured 13.5×8.5×8 cm, the tumor's dimensions were 6.5×10×7 cm, and histopathological examination revealed a renal cell carcinoma of the clear cell type (G2). The staging was pT3, N2, M1. At the time of nephrectomy, multiple metastases to the lungs of 1.5 cm or more in diameter were noted. On February 27, alternate-day subcutaneous therapy with OK-432 (5 KE) and intravenous therapy

with alpha interferon (3,000,000 units) were instituted. The patient was discharged on June 26, and alternate-day injection of the same drugs was continued on an outpatient basis. Because the patient's posterior longitudinal ligament sclerosis deteriorated and visits to the outpatient clinic became more difficult, he was again admitted on August 5. After admission alternate-day subcutaneous OK-432 (5 KE) and intravenous alpha interferon (3,000,000 units) were again instituted, but the pulmonary metastases gradually grew larger. On September 22, right hip pain developed and a pathological fracture of the neck of the right femur due to metastasis was detected on X-ray. He was transferred to this institution's orthopedic department where the head of the femur was replaced with an artificial prosthesis. The bone lesion showed a favorable course, and the patient was transferred back to this department on November 25. At that time the dose of alpha interferon was increased to 6,000,000 units, but his pulmonary metastases gradually grew larger (Fig. 1A). CT examination in March 1988 revealed coin lesions in the lung fields approximately 3 cm in diameter (Fig. 1B). For this reason, alpha interferon administration was discontinued, and daily therapy was commenced

with r-IL-2 (1,000,000 units) divided into 2 doses and administered dissolved in 100

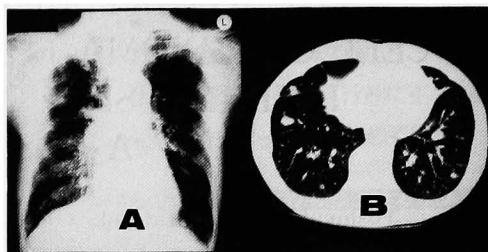


Fig. 1. Plain chest X-ray (A) and chest CT scan (B) from the patient prior to initiation of r-IL-2 administration revealing multiple coin lesions in the lung fields.

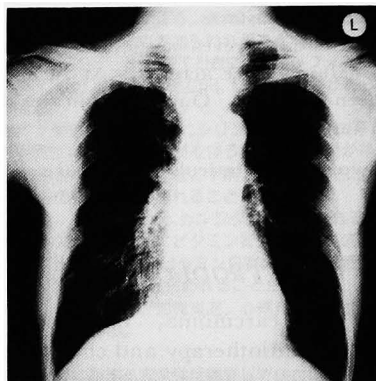


Fig. 2. Plain chest X-ray 5 months after discontinuation of r-IL-2 shows no evidence of recurrence in the lungs

CASE H.T. 68yrs. M Multiple Pulmonary Metastases of Renal Cell Carcinoma

PRETREATMENT: Transperitoneal right radical nephrectomy(pT₃N₂M₁) (23.2.'87)

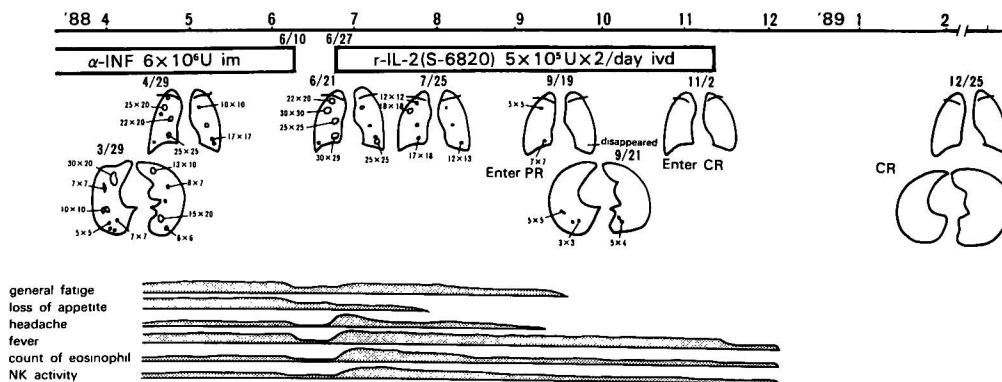


Fig. 3. Clinical course and investigation results for the patient

ml of physiological saline by intravenous infusion over approximately a 2-hour period. Shrinkage of the pulmonary metastases was noted 1 month later, and after 2.5 months of treatment, all metastases had disappeared except for 2 rather large lesions. Complete disappearance of all the metastases was observed after 4 months of treatment and r-IL-2 was then discontinued (Fig. 2). At the present time, 16 months after discontinuation of the drug, no recurrences have been observed in either the lung or the femur.

Fig. 3 shows the patient's post-nephrectomy clinical course and investigation results. BUN was within normal limits both before and after r-IL-2 administration, while GOT rose slightly after administration, but returned to normal 2.5 months later. Among the immunological tests performed, the eosinophil count was elevated and increased NK activity was detected. Among the lymphocyte subsets, OKT8 and OKLa1 were increased and OKT4, OKT3 and B1 tended to be reduced. Fever of 38°C or more and generalized fatigue were noted; however, his appetite was better than during the period of alpha interferon administration. No serious side effects were observed.

DISCUSSION

Because renal cell carcinoma metastases sometimes disappear after resection of the primary focus, and while sometimes metastatic foci appear long after primary tumor resection, renal cell carcinoma appears to be a special tumor exhibiting an immunological relationship between host and tumor. In 1982, Grimm et al.⁷⁾ reported induction of LAK cells which damage the patients' own cancer cells which they obtained by culture of peripheral blood lymphocytes from cancer patients in media containing IL-2. In 1987, Rosenberg et al.⁸⁾ reported observing complete regression (CR) or partial regression (PR) in 12 out of 36 patients with renal cell carcinoma treated with a combination of in vitro-induced LAK cells and r-IL-2. Various other reports have been made, e.g., com-

bination therapy with LAK cells and IL-2 (Fisher⁹⁾, Wang¹⁰⁾, Belldegrum¹¹⁾), high-dose IL-2 monotherapy (West¹²⁾) and low-dose IL-2 therapy (Sosman¹³⁾), and PR or better efficacy rates of 16 % to 50 % have been shown. However, there are few reports of CR: 4 out of 36 cases from the series of Rosenberg et al.⁸⁾ (combined LAK and r-IL-2 therapy) plus 1 case out of 36 from a series given high dose r-IL-2 monotherapy, plus 2 cases out of 35 from the series of Fisher et al.⁹⁾ (combined LAK and r-IL-2 therapy). These add up to just 7 cases. In Japan, Ikemoto et al.¹⁴⁾ reported 1 case in which PR was obtained. Marumo¹⁵⁾ administered r-IL-2 to 12 patients with renal cell carcinoma and obtained a CR in 2 of them (16.7%) and PR in 1. Aso et al.¹⁶⁾ completed treatment of r-IL-2 for 60 patients with advanced renal cell carcinoma, and obtained an efficacy rate of 15% (CR and PR). Fujioka et al.¹⁷⁾ administered r-IL-2 to 14 patients with advanced renal cell carcinoma and obtained a PR in 1 case. They also emphasized that the response rate increased to 12.5% in cases with pulmonary metastases alone. This finding is also founded by Aso et al.¹⁶⁾ They suggested two reasons for the good efficacy of IL-2 against lung metastasis. One is that the antineoplastic activity of IL-2 depends on the biological characteristics and heterogeneity of lung metastasis, and the other is that the lung provides a favorable environment for the anti-tumor activity of IL-2.

The predominant susceptibility of pulmonary metastasis to alpha interferon was also made clear by Umeda et al.⁴⁾

In any event, there are extremely few reported cases of CR in advanced renal cell carcinoma treated with IL-2.

The mechanism of the antineoplastic effect of IL-2 is generally believed to lie in the induction/activation of NK and LAK cells in vivo. Increased NK activity was detected in our own patient immediately after IL-2 administration, and this finding is consistent with the line of thinking described above. The antitumor effect of alpha interferon is also claimed to be explainable on an immunological basis.

Table 1. Toxities of r-IL-2

Reporter total patients	Wang et al ¹⁰⁾ 13		Sosman et al ¹³⁾ 32		Fisher et al ⁹⁾ 35		Aso et al ¹⁶⁾ 60	
Toxity	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Fever	13	100	30	94	—	—	10	17
Fatigue	13	100	—	—	—	—	13	22
Chills	13	100	—	—	—	—	13	22
Edema	12	92	8	25	20	57	2	3
Hypotention	11	85	14	44	26	74	—	—
Nausea and vomiting	13	100	14	44	—	—	7	12
Anemia	13	100	2	6	25	71	5	8
Eosinophilia	13	100	—	—	—	—	40	67
Lukocytosis	—	—	—	—	—	—	29	48
Creatinin elevation	6	46	2	6	15	45	2	3
BUN elevation	—	—	—	—	—	—	3	5
Hyperbilirubinemia	2	15	0	0	4	11	—	—
SGOT, SGPT elevation	—	—	—	—	17	48	10	17

Our case showed no response to long-term alpha interferon, but showed a marked response to r-IL-2. The reason why CR was obtained by r-IL-2 following treatment with interferon is not clear.

Table 1 summarizes the toxic effects of IL-2 associated with treatment for advanced renal cell carcinoma.

In our own case, the toxic effects were fever, general fatigue, and an elevation of leukocyte count (lymphocytes, eosinophils). These effects abated shortly after IL-2 was discontinued. Other serious adverse effects, such as liver or renal function disorders, and hypotension were not observed. The patient's appetite was actually better than during the period of alpha interferon administration. Intravenous infusion of r-IL-2 is relatively easy to perform, and we intend to treat more cases in this way.

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和文抄録

r-Interleukin 2 点滴静注により多発性肺転移が完全消失した腎細胞癌の1例

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r-IL-2 を点滴静注することにより, α -interferon に抵抗を示した腎細胞癌の多発性肺転移が完全に消失した症例を経験したので報告する。

症例は68歳, 男性。1987年1月に顕微鏡的血尿を認めたため IVP および 腹部 CT を行ったところ右腎に腫瘤を認めたため入院となり, 2月23日, 経腹膜の根治的右腎摘除術を行った。摘出腎は $13.5 \times 8.5 \times 8$ cm, 腫瘍は $6.5 \times 10 \times 7$ cm であり, 病理組織学的所見は renal cell carcinoma, clear cell type, G2 であり, 進展度は pT3N2M1 であった。腎摘除時にす

で肺に直径 1.5 cm 以下の多発性転移を認めた。2月27日より OK-432 (5KE) および α -interferon (300万→600万単位) の隔日注射を開始したが, 肺転移像は徐々に増大した。 α -interferon の投与は無効と判断し, 6月27日より r-IL-2 (100万単位) の点滴静注を開始した。1カ月後には肺転移像の縮小を認め, 2.5カ月後には比較的大きな2個の転移部を除き他は消失し, さらに4カ月後には肺転移像の完全消失を認めたため, r-IL-2 の投与を中止した。投与中止後16カ月経過した現在, 再燃を認めない。

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