Tokai J Exp Clin Med., Vol. 30, No. 2, pp. 111-115, 2005

Successful Treatment of Renal Cell Carcinoma With Mediastinal Lymph Node Metastasis by Interleukin-2: A case report

Masatoshi TOKUNAGA, Aiichiro MASUDA, Masaya MUKAI[*],
Hideyuki NAKAMURA[***], Koji IWAKI[****], and Toshiro TERACHI[**]

Departments of Urology and [*]Surgery, Tokai University Oiso Hospital
[**]Department of Urology, Tokai University School of Medicine
[***]Department of Medical Information, Schering-Plough K.K
[****]SRL, Inc.

(Received January 17, 2005; Accepted April 18, 2005)

A 57-year-old woman presented to our hospital with macrohematuria. Renal cell carcinoma (RCC) of the left kidney with bilateral pulmonary and mediastinal lymph node metastases was diagnosed. Radical nephrectomy was performed. Pathological examination confirmed the diagnosis of RCC (pT2pN0M1), so immunotherapy was performed using interleukin-2 (IL-2). The mediastinal lymph node metastases disappeared completely after 5 months of immunotherapy. Investigation of immunological parameters showed an increase of CD8-positive T cells (CD8) and a decrease of CD14-positive cells (CD14), leading to a marked increase of the CD8/CD14 ratio. Although her pulmonary metastases are unchanged, the mediastinal metastases still show complete remission at 14 months postoperatively. The CD8/CD14 ratio may have potential as a new marker for monitoring the response of RCC to immunotherapy and selecting suitable patients for such therapy.

Key words: metastatic renal cell carcinoma, IL-2, immunological parameter, CD8/CD14 ratio

INTRODUCTION

Renal cell carcinoma (RCC) is associated with distant metastasis in about 28% of patients at first presentation [1]. Patients who have metastatic disease are often treated with immunotherapy followed by radical nephrectomy, although this is only effective in about 5 to 20% [2]. Since no standard immunotherapy protocol has been established, the agents and their doses are decided by the attending physician. A previous study showed that various immunological parameters increase after immunotherapy [3], although the relationship between these parameters and the clinical outcome was unclear.

Here we report a patient who had RCC with mediastinal lymph node metastasis that responded to treatment with interleukin-2 (IL-2: Imunace®35, Shionogi Pharmaceutical Co., Ltd., Osaka, Japan). We also discuss the relationship between the response to IL-2 and several immunological parameters.

CLINICAL SUMMARY

The patient was a 57-year-old woman who presented to our hospital with macrohematuria on September 12, 2002. At that time, her general condition was good and there were no abnormalities on physical examination. Laboratory values were normal, except for a hemoglobin of 12.6 g/dl that indicated mild anemia. Abdominal computed tomography (CT) showed a tumor with a diameter of 9 cm at the lower pole of the left kidney (Fig. 1), as well as mediastinal lymph node enlargement (Fig. 2a) and bilateral multiple pulmonary metastases. Accordingly, she was diagnosed as having metastatic RCC (T2N0M1) and underwent left radical nephrectomy on November 8, 2002. Histopathological examination gave a

Aiichiro MASUDA, Department of Urology, Tokai University Oiso Hospital, Gakkyou 21-1, Oiso, Kanagawa 259-0198, Japan
Tel: +81-463-72-3211 Fax: +81-463-72-2256 E-mail: toku@is.icc.u-tokai.ac.jp

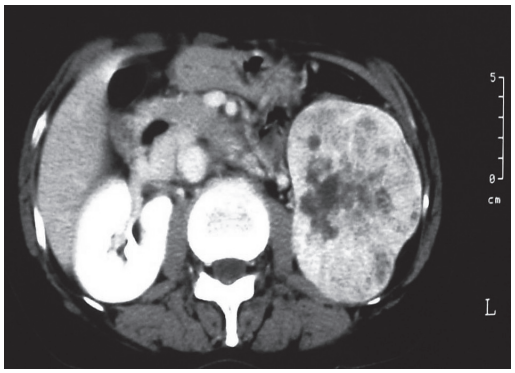

Fig. 1 Abdominal CT scan shows a tumor with a diameter of 9 cm at the lower pole of the left kidney.

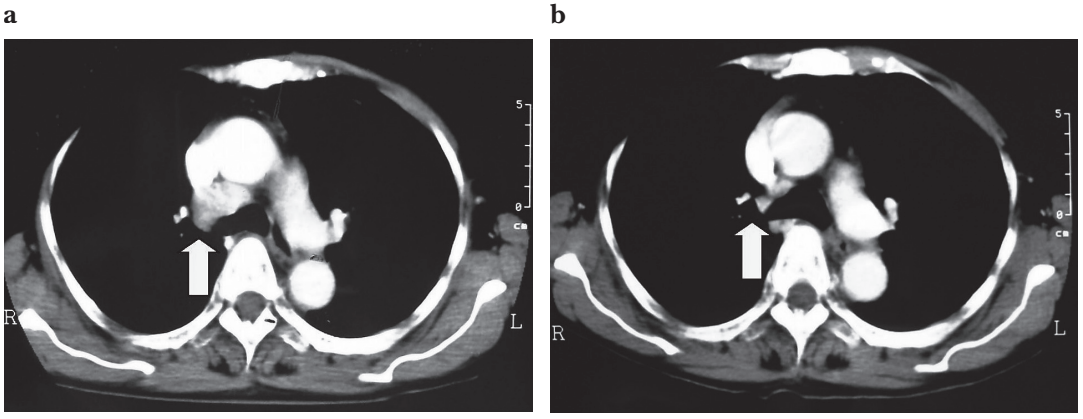

Fig. 2 **a**: Chest CT scan shows mediastinal lymphadenopathy.
b: Lymphadenopathy is no longer detectable at 5 months after the start of immunotherapy.

diagnosis of clear cell RCC (Grade 2, INF β, and v (-)), and the staging was pT2pN0M1. Her postoperative course was uneventful, so immunotherapy for the mediastinal lymph node and pulmonary metastases was started in December 2002. She received 0.7×10^6 JRU/day of IL-2 intravenously for 5 days per week, with 4 weeks of therapy being considered as 1 course. The dose of IL-2 was increased to 1.4×10^6 JRU/day in January 2003. After it was confirmed that adverse reactions did not occur, her immunotherapy was given on an outpatient basis. In May 2003, the regimen was modified to intravenous injection of 1.4×10^6 JRU of IL-2 twice weekly and intramuscular injection of 6×10^6 IU of interferon alfa-2b (IFNα-2b: Intron-A®, Schering-Plough K.K., Osaka, Japan.) three times a week (Fig. 3). Although there were no changes of the pulmonary metastases, her mediastinal lymph node metastases became completely undetectable on CT scans from 5 months after the start of immunotherapy (Fig. 2b).

Immunophenotyping

CD8-positive T cells (CD8) and CD14-positive cells (CD14) were identified in peripheral blood samples by flow cytometry, and the CD8/CD14 ratio was calculated. Analysis was done by measurement of forward scatter and side scatter using a lymphocyte gate for CD8 cells and a leukocyte gate for CD14 cells. Then the relationship between the CD8/CD14 ratio and the clinical course was examined (Fig. 4). The percentage of CD8 cells showed a gradual increase during treatment with IL-2, rising from 22.2% to 41.2% within 4 months after the start of immunotherapy. This percentage remained high (32.6%) after IL-2 therapy was suspended, so the patient's regimen was changed to improve her quality of life by reducing intravenous administration of IL-2

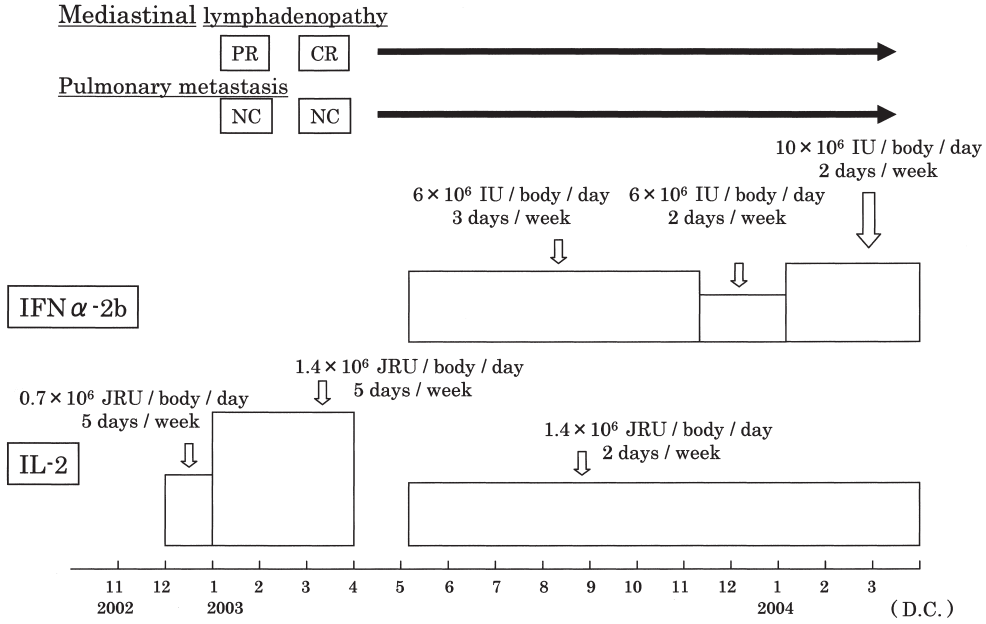

Fig. 3 Clinical course: Immunotherapy for the mediastinal lymph node and pulmonary metastases was started in December 2002. The patient received 0.7×10^6 JRU/day of IL-2 intravenously (5 days per week), repeated for 4 weeks as 1 course. The daily dose was increased to 1.4×10^6 JRU in January 2003. Although there were no changes of the pulmonary metastases, the mediastinal lymph node metastases could no longer be detected by CT from 5 months after the start of immunotherapy.

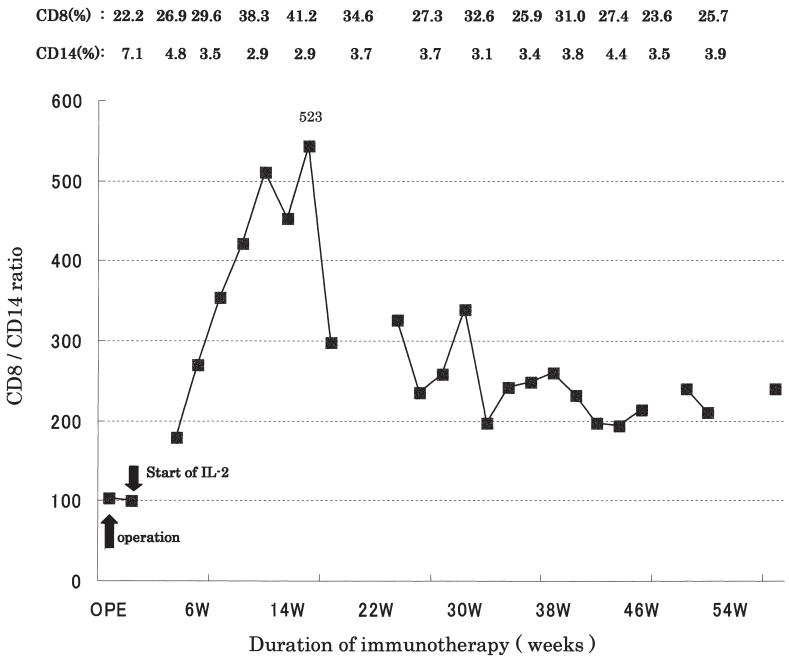

Fig. 4 Changes of the CD8/CD14 ratio were calculated by setting the ratio on the first day of immunotherapy as 100, and were plotted over time. CD8-positive cells increased and CD14-positive cells decreased during IL-2 administration, with the peak value of the ratio (523) occurring at 4 months after the start of immunotherapy.

to twice weekly and adding intramuscular IFNα-2b three times weekly. CD8 cells fluctuated in a range from 34.6% to 22.4% after the regimen was changed. CD14 cells tended to decrease from 6.8% at the time of surgery to a nadir of 2.4% around the time when CD8 cells reached their peak. CD14 cells ranged from 3.0% to 4.5% after the immunotherapy regimen was changed. When the CD8/CD14 ratio was calculated and the changes of this ratio (determined by setting the ratio on the first day of immunotherapy as 100) were plotted over time, the peak value of 523 was seen at 4 months after the start of IL-2 therapy. Mediastinal lymph node metastases were no longer detectable on the chest CT scan obtained 1 month after the CD8/CD14 ratio reached its maximum level.

DISCUSSION

With the widespread use of ultrasonic screening and progress in other imaging methods, detection of early RCC has increased. However, 28% of patients have distant metastasis at the time of presentation [1], and even pN0M0 tumors have a 50% risk of recurrence within 2 years after nephrectomy [4].

Immunotherapy has generally been performed in patients who have metastatic RCC or high-stage tumors. Immunotherapy ranks second after surgery because the host immune response is thought to have a greater influence on the growth of RCC compared with other cancers and because RCC shows a poor response to standard chemotherapy or radiotherapy. However, immunotherapy using IFNα and IL-2 is only effective for 17% of patients with metastatic RCC (i.e., achieves complete remission or partial remission) [5]. Although previous reports have indicated that immunotherapy can promote long-term survival [6] and can be very effective for pulmonary metastases [7], no standard regimen has been established and there is no agreement about the agents, doses, administration period, and treatment interval.

The host immune response to a tumor is quite complex. It is known that CD8-positive T lymphocytes are important because these cells can differentiate into cytotoxic T lymphocytes (CTL) that directly attack and kill tumor cells. A recent study showed that dendritic cells recognize tumor antigens, act as antigen-presenting cells (APC), and strongly activate T cells [8]. Monocytes (CD14 cells) are thought to differentiate into dendritic cells or macrophages in patients with a high level of CTL activity, resulting in a decrease of resting monocytes and an apparent decline of CD14 cells.

IL-2 is secreted by T cells and this cytokine induces CTL activity. However, we see little reduction of tumor size in many patients receiving IL-2 therapy despite an increase of CTL activity. Some studies of immunological parameters during immunotherapy have shown increased cytotoxic activity of natural killer cells and an increase of CD8 positive T cells [3], although it remains unclear how these changes are related to the clinical course. Fujimoto et al. reported that changes of the CD8/CD14 ratio could be used to predict the therapeutic efficacy and morbidity of immunotherapy [9]. However, they used different gates for flow cytometry, measuring CD8 positive T cells as leukocytes and CD14-positive monocytes as mononuclear cell. When we examined CD8-positive cells using a leukocyte gate and a mononuclear cell gate, contamination by granulocytes was observed. Therefore, to count CD8 positive T cells accurately, we employed a lymphocyte gate for flow cytometry. Although various immunological parameters have been examined in patients receiving immunotherapy for RCC, these parameters have not been useful to predict the response to immunotherapy. For the host immune response to occur, a tumor needs to be recognized as non-self by APC because tumor-specific antigens are expressed with major histocompatibility complex molecules, and the APC need to stimulate T cells. The dendritic cells that act as APC probably differentiate from CD14-positive cells (monocytes) and this indirectly leads to a reduction of the monocyte count. Our result suggest that the lack of an increase in the CD8/CD14 ratio might indicate the need to change the immunotherapy regimen for RCC, if this is taken as an index of the induction of tumor-specific immunity. Although a fundamental study has not yet demonstrated the relationship between a decrease of CD14 cells and an increase of dendritic cells, the CD8/CD14 ratio may have potential as a new indicator for assessing the effect of immunotherapy and selecting suitable patients for such therapy. To confirm the

significance of the CD8/CD14 ratio, however, further investigations will be needed in a larger number of patients to better define the clinical value of this parameter.

REFFERENCES

1) Onishi T, Machida F, Kurauchi H, Mori Y, Suzuki M, Iizuka N, Kondo I, Furuta N, and Shirakawa H: Nephrectomy in renal carcinoma with distant metastasis. Br J Urol 63: 600-604, 1989.
2) Northway RO, Ritenour CWN, and Marshall FF. Advances in the diagnosis and treatment of renal cell carcinoma. Int J Clin Oncol 5: 289-296, 2000.
3) Bohm M, Ittenson A, Schierbaum KF, Rohl FW, Ansorge S, and Allhoff EP. Pretreatment with interleukin-2 modulates peri-operative immunodysfunction in patients with renal cell carcinoma. Eur Urol 41: 458-468, 2002.
4) Masuda A, Aoki M, Tokunaga M, Usui Y, Abe T, Miyakita H, Kinoshita H, Kawamura N, and Terachi T. Clinicopathological factors predicting recurrence of N0M0 renal cell carcinoma: A case series analysis of one facility. Int J Urol 10: 511-517, 2003.
5) Dutcher JP, Logan T, Gordon M, Sosman J, Weiss G, Margolin K, Plasse T, Mier J, Lotze M, Clark J, and Atkins M. Phase II trial of interleukin 2, interferon α, and 5-fluorouracil in metastatic renal cell cancer: A Cytokine working group study. Clin Cancer Res 6: 3443-3450, 2000.
6) Kinoshita H, Arihara K, Masuda A, Hihara T, Kawamura N. Long term survival achieved using IL-2 in a case of pulmonary metastasis following surgery for renal carcinoma. Jpn Urol Surg 13: 1305-1310, 2000. (In Japanese)
7) Sakata Y, Ogura Y, Wakita T, Hayashi N, and Sugimura Y. Successful treatment for renal cell carcinoma with lung metastasis by interleukin-2 and interferon-alfa: A case report. Act Urol Jpn 49: 389-391, 2003. (In Japanese)
8) Renner C, Kubuschok B, Trumper L, and Pfreundschun M. Clinical approaches to vaccination oncology. Ann Hematol 80: 255-266, 2001.
9) Fujimoto S, Hamasato S. An essential immunological parameter predicting efficacy of anti-cancer therapy in advanced cancer patients. Biotherapy 12: 1427-1433, 1998. (In Japanese)