

Efficacy of IL-2 Immunotherapy in Metastatic Renal Cell Carcinoma in Relation to the Psychic Profile as Evaluated Using the Rorschach Test

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Abstract. *Background:* Despite the well-documented importance of the psycho-emotional status in modulating the anticancer immunity, at present no study has been performed to analyse the influence of the psychological condition on the efficacy of IL-2 cancer immunotherapy. Previous clinical studies have already suggested that the evidence of anxiety may negatively affect the therapeutic efficacy of IL-2 immunotherapy of cancer. Moreover, previous psycho-oncological investigations showed that the suppression of sexual pleasure and sexual identity would represent one of the most frequent psychological profiles in cancer patients. On this basis, a study was planned in an attempt to evaluate relations existing between psychological status, analysed using the Rorschach test and efficacy of IL-2 immunotherapy in the treatment of metastatic renal cell cancer patients. *Patients and Methods:* The study included 30 consecutive metastatic RCC patients. IL-2 was injected s.c. at a dose of 3 million IU twice/day 5 days/week for 4 consecutive weeks, corresponding to one complete immunotherapeutic cycle, followed by a second cycle after a 21-day rest period. *Results:* A complete response (CR) was achieved in only 1/30 (3%) patients; a partial response (PR) was obtained in 6/30 (20%) patients. The tumor response rate (CR+PR) was 7/30 (23%) patients. The performance of a psychological analysis was accepted by 24/30 (80%) patients. A normal sexual identity was present in 7/24 (29%) patients. The tumor response rate achieved in patients with sexual identity was significantly higher compared to these who had no sexual identity or who refused the psychological investigation ($p < 0.05$ and $p < 0.01$, respectively). In the same way, the increase in mean lymphocyte number obtained in patients with sexual

identity was significantly higher compared to that found in the other two groups of patients. *Conclusion:* This study demonstrated that the psychological status prior to treatment may be associated with the clinical response to IL-2 cancer immunotherapy.

Even though it is known that a patient's psychological status may influence the prognosis of the neoplastic disease, the investigation of the psychic profile is not generally included in the clinical management of cancer patients, or it is limited to the evaluation of patient compliance and quality of life. According to the data available, the psychological profile may be expected to affect the clinical history of cancer, mainly by influencing the immunity status of patients. In particular, it has been demonstrated that the secretion and the biological activity of interleukin-2 (IL-2), which is the main antitumor cytokine in humans, is inhibited by stress-related substances, such as catecholamines and opioid peptides, whereas these processes are stimulated by pleasure-related substances, namely pineal indoles, GABA and endocannabinoids (1-7). In fact, it is known that the antitumor efficacy of IL-2 does not depend on a direct action on cancer cell proliferation, but is due to the biological response of patients in an antitumor way induced by IL-2 itself (8). Moreover, according to the recent knowledge of psychoneuroimmunology, the immune responses, including anticancer immunity, are physiologically under psychoneuroendocrine control, which represents the chemical mediation of the emotions and of the states of consciousness. Finally, preliminary clinical studies have shown that anxiety negatively influences the clinical efficacy of IL-2 cancer immunotherapy (9). As far as the psychological profile of cancer patients is concerned, our previous clinical studies have shown that suppression of sexual interest and sexual identity, as evaluated using Rorschach test, would constitute one of the most evident cancer-related psychological characteristics (10).

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Table I. *Clinical characteristics of metastatic RCC patients.*

Characteristics	
Male/Female	24/6
Median age (years)	66 (41-81)
Median PS (Karnofsky's score)	90 (70-100)
Dominant metastasis sites	
nodes	4
bone	9
lung	14
liver	1
lung + liver	1
kidney	1

On this basis, a study was planned to evaluate which may exist between the presence of a maintained sexual identity at Rorschach test and the clinical response to IL-2 immunotherapy in metastatic renal cell carcinoma (RCC).

Patients and Methods

The study included 30 consecutive metastatic RCC patients. Eligibility criteria were as follows: histologically proven RCC, measurable lesions, no previous therapy for the metastatic disease, no brain metastasis, and no concomitant chronic treatment with drugs influencing the immune system, such as corticosteroids and opioids. The clinical characteristics of the patients are reported in Table I. IL-2 was injected *s.c.* at a dose of 3 million IU twice/day 5 days/week for 4 consecutive weeks, corresponding to one complete immunotherapeutic cycle. In non-progressing patients, a second cycle was planned after a 21-day rest period. The patients then underwent a maintenance treatment consisting of 5 days of therapy every month, until disease progression or toxicity. Patients were considered as evaluable when they received at least one complete immunotherapeutic cycle. The clinical response was assessed according to WHO criteria, undertaking radiological examination before the onset of immunotherapy, after each cycle of immunotherapy and then at 3-month intervals. Visceral metastases were evaluated using CT scan. For haematological analysis, venous blood samples were collected before therapy, at weekly intervals during the immunotherapeutic cycles and every 3 weeks during the rest period. Rorschach test is a projective personality assessment based on the test taker's reactions to a series of inkblot pictures. It is the most widely used projective psychological test. Rorschach test is used to help assess personality structure and identify emotional problems and mental disorders. It is based on the principle that subjects viewing neutral, ambiguous stimuli will project their own personalities on to them, there by revealing a variety of unconscious conflicts and motivations. Rorschach test is used to elicit information about the structure and dynamics of an individual functioning personality. The test provides information about a person's thought processes, perceptions, motivations and attitude towards their environment and can detect internal and external pressures and conflicts, as well as illogical or psychotic thought patterns.

Rorschach test is administered using 10 cards, each containing a complicated inkblot pattern, five in black and grey, two in black

Table II. *Clinical characteristics of metastatic RCC patients in relation to the Rorschach test.*

Characteristics	Presence of sexual identity	Lack of sexual identity	Refusal
N.	7	17	6
M/F	5/2	14/3	5/1
Median age (years)	64 (46-74)	69 (47-81)	68 (41-76)
Median PS* (Karnofsky's score)	90 (80-100)	90 (70-100)	90 (90-100)
Dominant metastasis sites			
node	1	1	2
bone	2	6	1
lung	4	8	2
liver	0	0	1
lung + liver	0	1	0
kidney	0	1	0

*PS: performance status.

and red, and three in various pastel colours. Subjects look at the cards one at a time and describe what each inkblot resembles. They are instructed to look at the shape, shading and colour of the inkblots. After the subject has viewed all 10 cards, the examiner usually goes back over the responses for additional information. The subject may be asked to clarify some responses or to describe which features of each inkblot prompted the responses. There is no correct response to any inkblot card, although there are certain common responses to some cards. Despite criticism, Rorschach test is considered to be able to adequately contribute to the psychological diagnosis and to the study of the more unconscious profile of the personality (11).

The results were statistically evaluated using the Chi-square test, Student's t-test and analysis of variance, when appropriate.

Results

The clinical characteristics of the patients are reported in Table I.

A complete response (CR) was achieved only in 1/30 (3%) patients. A partial response (PR) was obtained in 6/30 (20%) patients. Then tumor response rate (CR+PR) was 7/30 (23%) patients. A stable disease (SD) occurred in 14/30 (47%) patients, whereas the other 9/30 (30%) patients had a progressive disease (PD).

Rorschach test performance was accepted by 24/30 (80%) patients, whereas the remaining 6/30 (20%) patients refused the psychological investigation documented the presence of a normal sexual identity in only 7/24 (29%) patients who accepted the psychological analysis. The clinical characteristics of patients in relation to the response to the test are reported in Table II. As shown, the three groups of patients with a maintenance of sexual identity, with a lack of

Table III. Clinical response (WHO criteria) to IL-2 immunotherapy in relation to the Rorschach test in metastatic renal cell cancer patients.

Patients Rorschach test result	n	Clinical response ⁺					
		CR	PR	CR + PR (%)	SD	DC (CR+PR+SD) (%)	PD (%)
No sexual identity	17	0	3	3 (18%)	10	13 (76%)	4 (24%)
Sexual identity	7	1	3	4 (57%)*	3	7 (100%)	0
Refusal	6	0	0	0	1	1 (17%)	5 (83%)

⁺CR: complete response; PR: partial response; SD: stable disease; DC: disease control; PD: progressive disease. **p*<0.05 sexual vs. no sexual identity, *p*<0.01 sexual identity vs. refusal.

sexual identity or who refused the psychological investigation were well-balanced for the overall main prognostic variables, including age, (PS) and dominant metastasis sites. Table III shows the clinical response to IL-2 immunotherapy in relation to the psychological profile. The tumor response rate obtained in patients with sexual identity was significantly higher with respect to these patients who had no sexual identity or who refused the psychological investigation (*p*<0.05 and *p*<0.01, respectively).

As far as the immunobiological response is concerned, as illustrated in Figure 1, the mean number of lymphocytes observed before the onset of treatment was higher in patients with sexual identity than in those without or those who refused the Rorschach test, without, however, statistically significant differences. On the contrary, the mean maximal lymphocyte count achieved in IL-2 immunotherapy in patients with sexual identity was significantly higher with respect to that observed in patient who had no sexual identity or who refused the psychological analysis (*p*<0.01 and *p*<0.001, respectively). The mean increase in lymphocyte number observed during IL-2 immunotherapy is illustrated in Figure 2. The value observed in patients with a maintenance of sexual identity was significantly higher with respect to that observed in patients who had no sexual identity or who refused the psychological test (*p*<0.05 and *p*<0.005, respectively) (11).

Discussion

This study shows that the lack of sexual identity, as assessed using the Rorschach test, is associated with a reduced efficacy of IL-2 immunotherapy in metastatic RCC patients in terms of both lymphocyte increase and disease-control, by confirming the influence of the psychological status on the anticancer immune response. The worse efficacy was observed in patients who refused the psychological investigation, since most of them had a rapid progressive disease in response to IL-2. This finding would probably depend on the existence of the profound repression of the emotions in those patients who refused to undergo the test.

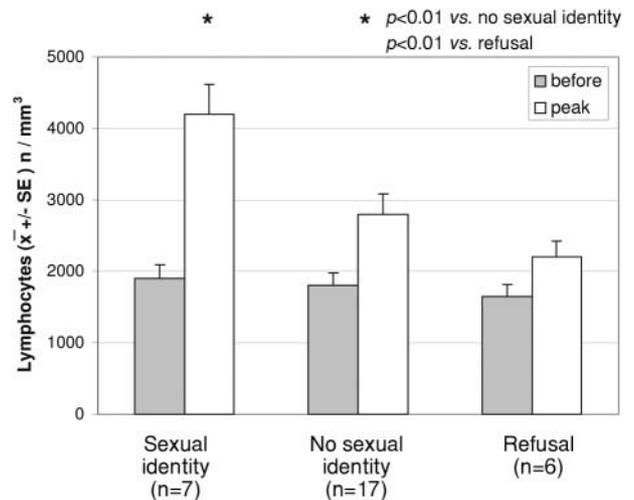


Figure 1. Mean lymphocyte number before the onset of treatment and mean maximum values during IL-2 immunotherapy in metastatic renal cell cancer in relation to the response to the Rorschach test.

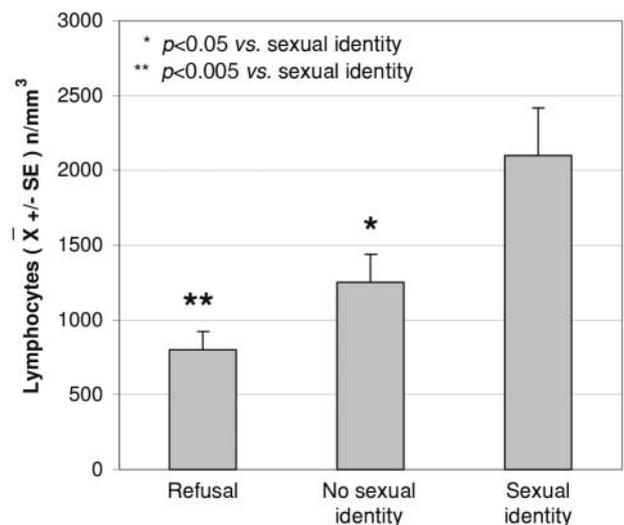


Figure 2. Mean maximum increase in lymphocyte number observed during IL-2 immunotherapy in metastatic renal cell cancer in relation to the response to the Rorschach test.

Therefore, the evaluation of the psychological status prior to treatment may predict the clinical response to IL-2 cancer immunotherapy. Obviously a great number of patients will be required to confirm these data. Moreover further study will be required in patients suffering from neoplasms other than RCC to establish whether their psychological status may influence the efficacy of IL-2 immunotherapy in RCC only, or whether it may be considered as a prognostic variable for the human tumours overall. In any case, the results of this psychoimmunological study demonstrated that the psychic condition influences immune reactions, in particular that lymphocyte proliferation in response to IL-2 is affected by the presence or absence of the consciousness of sexual identity. The importance of the sexual profile is not generally taken into consideration by psychologists, whereas the role of stress and anxiety on the immune response is well-known (9, 11-15). Therefore, further studying will be necessary to identify which is the most important variable within the great number of emotional parameters characterizing the psychological life of cancer patients.

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