Eur J Cancer, Vol. 28A, No. 10, pp. 1770–1771, 1992.
Printed in Great Britain
0964–1947/92 $5.00 + 0.00

Recombinant Interleukin 2 for Metastatic Renal Cell Carcinoma in Haemodialysis Patients

J. Buter, R.A.J. Janssen, N.H. Mulder, P.E. de Jong, L. de Leij and D.Th. Sleijfer

RECOMBINANT INTERLEUKIN 2 (IL-2) has opened a new approach in the treatment of renal cell carcinoma [1]. Because of the severe toxicity related to intravenous IL-2, this therapy appears only suitable for fit patients in which special attention is given to renal, cardiovascular and pulmonary function. Many patients with renal cell carcinoma are therefore not eligible for intravenous IL-2 treatment. Subcutaneously administered IL-2 alone, or combined with interferon alfa on an outpatient basis, can induce tumour regression in up to 20% [2–6]. Toxicity consists of fever and chills, local inflammation, anorexia, nausea, vomiting and hypotension. None of these side-effects requires hospitalisation, and are acceptable even in patients with major organ disfunction. We describe here the application of a subcutaneous IL-2 regimen in two patients on haemodialysis, with special emphasis on toxicity and immunological parameters.

The first patient, male, born in 1934, underwent a nephrectomy of the right kidney (1965) for nephrolithiasis and of the left kidney for a renal cell carcinoma (1989), followed by dialysis, which was complicated by ventricular and supraventricular ectopic arrhythmias. The second patient, male, born in 1915, underwent a nephrectomy for a renal cell cancer of the left (1980) and of the right kidney (1986). Subcutaneous IL-2 (EuroCetus) was started for progressive lung metastases in both patients in a 5-day cycle, every week for 6 weeks, at a dose of 18×10^6 I.U. daily in the first cycle, while the dose in the first 2 days of the following cycles was reduced to 9×10^6 U; both patients received paracetamol. Toxicity of IL-2 consisted of transient inflammation and local induration at the injection sites, fever and chills WHO grade II, anorexia, nausea, vomiting and diarrhoea grade I, an increase in serum levels of alkaline phosphatase to 409 and 179 U/l, respectively ($n \leq 120$), lactate dehydrogenase to 416 and 327 U/l ($n \leq 235$) and gamma-glutamyl transferase to 300 and 158 U/l ($n \leq 65$). The leucocyte count rose to a maximum of 16.2 and 27.3 $\times$ 10^9/l, respectively (n = 4.0–11.0). Blood pressure decreased to a lowest value of 90/60 and 75/50 mmHg, respectively. No vasopressors were used. Fluid retention, weight gain and nephrotoxicity could not be evaluated because of the haemodialysis, which was continued two times a week in both patients and later, three times a week in the first patient because of uraemic pericarditis. After 6 weeks of treatment, restaging showed progressive disease in the first and a stable disease in the second patient. Lymphocyte subsets were determined by flow cytometry using the monoclonal antibodies (Mab) Leu4-FITC, Leu3-FITC, Leu2-FITC/PE, Leu19-PE/unlabelled, anti-HLA-Dr-FITC/PE and anti-IL-2Ralfa-FITC/PE (Becton Dickinson). Soluble IL-2 receptor (IL-2R) in serum was measured by a sandwich enzyme-linked immunosorbent assay (T-cell Sciences, Cambridge Massachusetts). Immunological changes are listed in Table 1.

Table 1. Immunological changes during IL-2 therapy

Variable*	Patient 1	Patient 2
No. of CD3+ cells 10^3/ml		
Baseline	350	370
Peak	880	2380
After treatment	670	1130
No. of CD56+CD3− cells 10^3/ml		
Baseline	50	90
Peak	500	1210
After treatment†	500	780
CD3+HLA−Dr+† 5(3%)‡		
Baseline	14	15
Peak	34	57
CD56+HLA−Dr+† 4(3%)		
Baseline	27	25
Peak	74	52
CD3+CD25+† 3(2%)		
Baseline	19	8
Peak	36	56
Soluble IL-R (69–477 U/ml)		
Baseline	2541	1521
Peak	24775	22268

*Normal values in parentheses.
† Expressed as percentage of the CD3+ or CD56+ subset, respectively.
‡ Mean (S.D.).

Toxicity of subcutaneous IL-2 in both patients described here was comparable to the toxicity in other patients treated with the same out-patient schedule, except for the somewhat more pronounced hypotension. Although in both patients an objective tumour regression was not found after 6 weeks of treatment, subcutaneously administered IL-2 induced immunological changes similar to those seen after IL-2 therapy in other patients [2, 6–8], and suggests that subcutaneously given IL-2 induces peripheral blood LAK activity in these patients.

Correspondence to D.Th. Sleijfer.
D.Th. Sleijfer is at the Department of Internal Medicine, University Hospital, Oostersingel 59, 9713 EZ Groningen, The Netherlands; J. Buter, N.H. Mulder and D.Th. Sleijfer are at the Department of Medical Oncology; R.A. J. Janssen and L. de Leij are at the Department of Immunology; and P.E. de Jong is at the Department of Nephrology, University Hospital Groningen, The Netherlands.
Revised 16 Mar. 1992; accepted 18 Mar. 1992.

1. Rosenberg SA, Lotze MT, Muul LM, *et al.* A progress report on the treatment of 157 patients with advanced cancer using lymphokine activated killer cells and interleukin-2 or high dose interleukin-2 alone. *N Engl J Med* 1987, **316**, 889–897.
2. Sleijfer DTh, Janssen RAJ, Willemse PHB, *et al.* Low dose regimen of interleukin-2 for metastatic renal carcinoma. *Lancet* 1990, **335**, 1522.

3. Atzpodien J, Korfer A, Franks CR, Poliwoda H, Kirchner H. Home therapy with recombinant interleukin-2 and interferon-alfa2b in advanced human malignancies. *Lancet* 1990, **335**, 1509–1512.
4. Stein RC, Malkovska V, Morgan S, *et al.* The clinical effects of prolonged treatment of patients with advanced cancer with low dose subcutaneous interleukin 2. *Br J Cancer* 1991, **63**, 275–278.
5. Whitehead RP, Ward D, Hemmingway L, Hemstreet III GP, Bradly E, Konrad M. Subcutaneous interleukin 2 in a dose escalating regimen in patients with metastatic renal cell adenocarcinoma. *Cancer Res* 1990, **50**, 6708–6715.
6. Sosman JA, Kohler PC, Hank JA, *et al.* Repetitive weekly cycles of interleukin-2. II clinical and immunological effects of dose, schedule, and addition of indomethacin. *J Natl Cancer Inst* 1988, **80**, 1451–1461.
7. Weil-Hillman G, Fisch P, Prieve AF, Sosman JA, Hank JA, Sondel PM. Lymphokine activated killer activity induced by *in vivo* interleukin 2 therapy: Predominant role for lymphocytes with increased expression of CD2 and Leu19 antigens but negative expression of CD16 antigens. *Cancer Res* 1989, **49**, 3680–3688.
8. Urba WJ, Steis RG, Longo DL, *et al.* Immunomodulatory properties and toxicity of interleukin-2 in patients with cancer. *Cancer Res* 1990, **50**, 185–192.

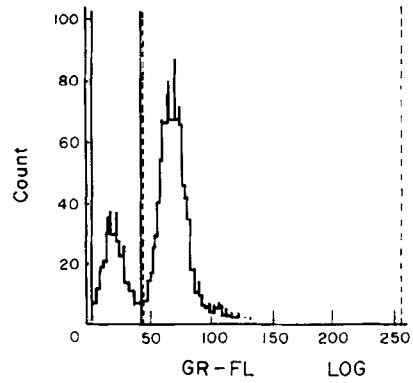

Fig. 1. CD10 intensity distribution in B-CLL patient.

Eur J Cancer, Vol. 28A, No. 10, p. 1771, 1992.
Printed in Great Britain
0964–1947/92 $5.00 + 0.00

CD10 Expression in B-chronic Lymphocytic Leukaemia

Stefano Molica and Angela Dattilo

IN B-CHRONIC lymphocytic leukaemia (B-CLL), rare CD10-positive cases have been reported [1–2]. Patrick *et al.* [1] observed transient CD10 expression in 38% of tested patients, associated with progressive disease. We have investigated CD10 expression in 39 B-CLL patients. There were 29 males and 10 females, average age 65.3 years (SD 8.2). According to Binet *et al.*'s staging [3], 22 patients were stage A, 10 were B and 7 were C. Immunophenotyping was done on peripheral blood cells. In all cases lymphocyte levels exceeded 5 3 10^9/1 and more than 75% of cells were CD5 and CD19 positive. Immunological studies were always done at the time of diagnosis. Fluorescence was read with a CYTORON cytofluorograph (Ortho Diagnostic System).

The results of peripheral blood cell phenotyping were [mean % (range)]: CD19, 77 (43.9–98.8); CD5, 71.8 (30–97.1); CD20, 61.4 (11–96.4); CD23, 75.1 (0.1–98); CD25, 48.6 (0.7–88.9); CD10, 37.4 (0.1–89.1); FMC7, 48.6 (0.5–80.6) and CD19/CD20, 1.8 (0.7–7.8).

A representative CD10 FACS profile is shown in Fig. 1, and suggests a CD10-positive population with weak fluorescence. CD10 density was always lower than that found in acute lymphoblastic leukaemia [mean fluorescence intensity was 84.9 (10.7) vs. 100.4 (11), respectively].

To investigate the clinical significance of CD10 expression in B-CLL, we analysed its relation with clinical stage and bone marrow histology. No significant correlation was found between CD10 expression and Binet *et al.*'s stages [stage A, 33.0% (31.7); B, 18.8% (30.1) and C, 32.5% (37.7); analysis of variance not significant]. The same applied when patients were analysed according to Rai *et al.*'s staging [4]. 11 patients with a non-diffuse bone marrow histology had a significantly higher number of CD10-positive cells [32.6% (30.5)] compared with 5 with a diffuse pattern [1.9% (2.6); $P < 0.02$].

Thus, CD10 can be expressed on cells of patients with othewise typical B-CLL. Kiyokawa *et al.* [5] have reported that CD10 is an activation antigen on mature B cells and is inducible by *in vitro* stimulation. However, expression patterns of CD10 and CD25 were different, suggesting expression in distinct phases of B cell activation. In our series CD10 and CD25 expression was not correlated, which is in agreement with the view that CD10 is an activation antigen transiently expressed at a very early stage of activation.

As for the relation between CD10 expression and clinical findings, our results suggest a correlation with the pattern of bone marrow involvement. Although our series was too small to draw firm conclusions, immunophenotyping including CD10 antigen may be a useful marker in detecting subgroups of CLL patients with different clinical features.

Correspondence to S. Molica at Via Casalinuovo, 6, 88100 Catanzaro, Italy.
A. Dattilo is at the Divisione di Ematologia, Ospedale Regionale "A. Pugliese", Catanzaro, Italy.
Revised 17 Feb. 1992; accepted 4 March 1992.

1. Patrick CW, Libnoch JA, Kallas G, Keller RH. Sequential immunophenotypic studies in chronic lymphocytic leukemia. In: Gale RP, Rai KR, eds. *Chronic Lymphocytic Leukemia: Recent Progress and Future Direction. UCLA Symposia on Molecular and Cellular Biology. New Series.* New York, Liss 1987, Vol. 59, 127–145.
2. Cacciola E, Giustolisi R, Guglielmo P. CALLA (CD10) positive lymphocytes in chronic lymphocytic leukemia. *Blood* 1989, **74** (suppl. 1), 340a.
3. Binet JL, Auquier A, Dighiero G, *et al.* A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer* 1981, **48**, 198–206.
4. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RM, Pasternak BS. Clinical staging of chronic lymphocytic leukemia. *Blood* 1975, **46**, 219–234.
5. Kiyakawa N, Kokay Y, Ishimoto K. Fujita H, Fujimoto J, Hata JI. Characterization of the common acute lymphoblastic leukemia antigen (CD10) as an activation molecule on mature human B cells. *Clin Exp Immunol* 1990, **79**, 322–327.