Soluble tumour necrosis factor receptors as prognostic factors in cancer patients

SIR—Two distinct types of soluble tumour necrosis factor receptors (sTNF-Rs), which are thought to represent proteolytic cleavage products of the extracellular domains of membrane-bound TNF-Rs of molecular mass 55 kDa (sTNF-RI) and 75 kDa (sTNF-RII), are found in the serum and urine of human beings. We measured the serum concentrations of sTNF-RI in 99 patients with advanced cancer (91 with renal cell carcinoma, 4 with melanoma, 4 with other solid tumours) before treatment with interleukin-2-based immunotherapy.

As noted by Aderka and colleagues,[1] we found raised sTNF-RI in cancer patients compared with normal controls (5·39 [2·35] ng/mL *vs* 2·67 [0·69] ng/mL, p=0·0001). An apparent correlation was observed between sTNF-RI and clinical and laboratory parameters that indicate progression of disease (Eastern Cooperative Oncology Group performance status ≥1, p=0·033; weight loss ≥5 kg, p=0·0056; erythrocyte sedimentation rate, p=0·0003; C-reactive protein, p=0·0001). Serum concentrations of sTNF-RI correlated inversely with serum albumin (p=0·0001) and haemoglobin (p=0·0168) concentrations.

Aderka et al[1] also observed a strong correlation between sTNF-R concentration and staging of disease. To investigate whether the prognosis of cancer patients can be predicted by the concentrations of their sTNF-Rs, we analysed progression-free survival times in subgroups of patients with sTNF-RI less than 6·5 ng/mL (n=76, group 1) or 6·5 ng/mL or more (n=23, group 2) (figure). Survival analysis according to the Kaplan-Meier method showed longer progression-free survival in patients with sTNF-RI less than 6·5 ng/mL (Mantel Cox p=0·0017, Tarone Wave p=0·0039, Breslow p=0·0101). Median progression-free survival of patients with low pretreatment sTNF-R concentrations was 10·6 months. Patients with high sTNF-R levels reached a median survival of 3·6 months.

The mechanisms involved in the increase of sTNF-R in cancer patients, as well as the functional implications, remain to be elucidated. Earlier studies suggest that excessive amounts of receptors in the sera of cancer patients are produced by the tumour cells themselves.[2] There is evidence, primarily from in-vitro studies, that tumour cells have a greater tendency than non-malignant cells to produce and shed soluble forms of their cell surface proteins.[3] So it

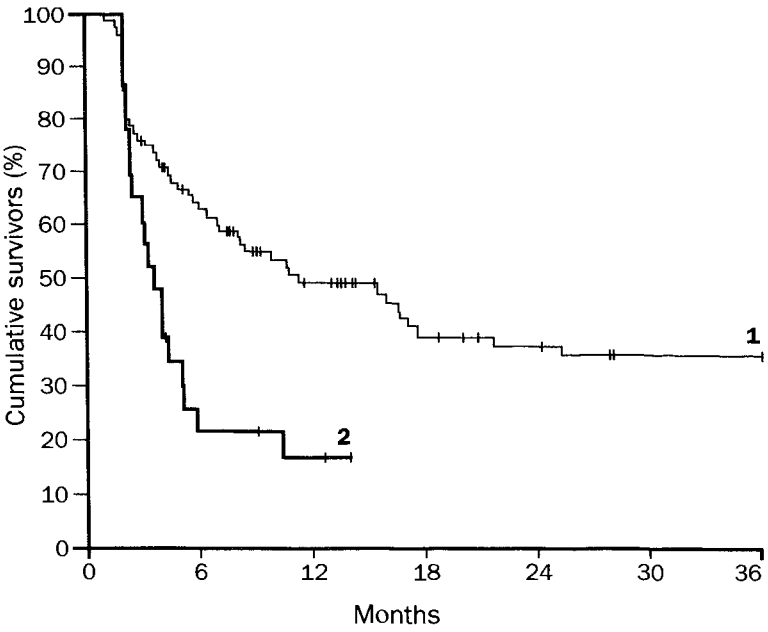

Figure: **Progression-free survival since treatment initiation**

Patients with sTNF-RI < 6·5 ng/mL (1) and ≥ 6·5 ng/mL (2).

seems possible that the increased concentrations of sTNF-R in cancer patients represent a tumour "escape" mechanism from the destructive effects of TNFα produced endogenously in respone to tumour antigens[4] and to interleukin-2 treatment.[5] However, our results suggest that sTNF-Rs may have a role as prognostic factors in cancer patients.

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