Eur J Cancer, Vol. 29A, No. 6, p. 928, 1993.
Printed in Great Britain
0964–1947/93 $6.00 + 0.00

Response of Soluble IL-2 Receptor Levels to Repeated Cycles of IL-2 Immunotherapy/Chemotherapy

E.M. Spiers, R.C. Potts, S.Y. Sharpe, E.L. Newman, M. Lavelle-Jones, J. Swanson Beck and A. Cuschieri

INTERLEUKIN-2 (IL-2) INFUSION alone or in combination with other agents can be effective in the treatment of certain human cancers [1]. After infusion, circulating lymphocyte numbers fall (as these cells initially become sequestered in the tissues) and then rebound, with a high proportion now expressing the receptor for IL-2 [2]. Soluble IL-2 receptors (sIL-2R) can also be detected in the blood of patients receiving IL-2 therapy, levels rising rapidly after bolus or continuous administration [3]. These molecules, by binding the cytokine, may possibly serve to limit the cellular response [4]. We wished to study these responses to repeated treatment with IL-2, to observe what longer term patterns there might be.

In 1989/1990, selected patients with metastatic colorectal cancer in the liver were entered in a study organised by Euro-Cetus (trial number EC-MP-004). This was designed to investigate the effect of repetitive cycles of recombinant IL-2 (proleukin) therapy and sequential chemotherapy with 5-fluorouracil (5-FU); a protocol which had previously been shown to confer some benefit in a small phase II trial[5]. In each cycle, a total of 90×10^6 U (15×10^6 Cetus U)/m^2 IL-2 were administered by constant infusion into a central vein over a 5-day period (days 1–5), followed by an intravenous injection of 5-FU (600 mg/m^2) on day 8. The 5-FU injection was repeated on days 15 and 22. The cycle was then repeated (i.e. starting IL-2 infusion on day 29). Since proleukin is hydrophobic, 0.25% human albumin was added to the infusion from the sixth treatment cycle onwards to minimise losses from adsorption to the syringe and catheter. Circulating lymphocytes were counted and soluble sIL-2R assayed on days 3 and 5 (during IL-2 infusion) and 8, 15 and 22 (immediately before 5-FU injection).

The results for 1 patient who underwent 14 cycles of treatment are shown in Fig. 1. The total lymphocyte count fell during each IL-2 infusion and then rebounded to higher levels (the CD4$^+$ and CD8$^+$ subsets behaved similarly, data not shown). The proportion of lymphocytes bearing the IL-2 receptor also rose from an already elevated level (10% of total compared with a normal range of < 1%) [6]. sIL-2R levels also rose during each cycle and at a time when circulating lymphocyte numbers were falling. This presumably represents activation of tissue-associated lymphocytes and diffusion of sIL-2R into the blood-

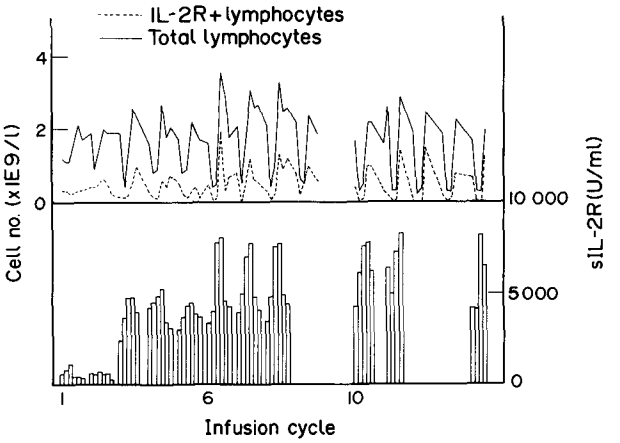

Fig. 1. Soluble IL-2 receptor levels (lower panel) and total and IL-2 receptor-bearing lymphocyte counts (upper panel). Each treatment cycle lasted for 4 weeks. There was a period of 3 weeks when no treatment was given, between cycles nine and 10. Albumin was added to the IL-2 infusion from cycle six onwards. Soluble IL-2 receptor was not assayed in cycles nine, 12 and 13.

stream. Responses became particularly marked after the first two cycles and further increased when albumin-containing infusions were initiated at cycle six. Adsorptive losses of IL-2 can clearly lead to a blunted response and should be minimised by providing a carrier protein. Responses to a given regimen soon became reproducible (cycles three to five are similar, as are cycles six to nine). IL-2 receptor levels remained high during cycles three to eight. This may suggest that "saturation" has been reached, and that a lesser dose might maintain the same effect. There was a gap in treatment of 3 weeks between cycles nine and 10 but basal sIL-2R levels were still high at the start of cycle 10 and increased to values comparable to those in previous cycles.

The effect of albumin and the temporal relationship between circulating sIL-2R levels and lymphocyte numbers were also seen in another 6 patients (data not shown). We believe that, in general, a number of treatment cycles is required before the full effect of intravenous IL-2 is observed and that addition of albumin enhances its biological availability. Further treatment results in long-term readjustments in sIL-2R levels and cellular responses to the infusion, which should be taken into account when designing new treatment protocols.

Correspondence to E.L. Newman.
E.M. Spiers, R.C. Potts and J. Swanson Beck are at the Department of Pathology; and S.Y. Sharpe, E.L. Newman, M. Lavelle-Jones and A. Cuschieri are at the Department of Surgery, Ninewells Hospital and Medical School, Dundee DD1 9SY, U.K.
Revised 19 Oct. 1992; accepted 10 Nov. 1992.

1. Borden EC, Sondel PM. Lymphokines and cytokines as cancer treatment. Immunotherapy realized. *Cancer* 1990, **65**, 800–814.
2. Lotze MT, Matory YL, Ettinghausen SE, *et al. In vivo* administration of purified human interleukin-2. II. Half-life, immunologic affects and expansion of peripheral lymphoid cells *in vivo* with recombinant IL-2. *J. Immunology* 1985, **135**, 2865–2875.
3. Lotze MT, Custer MC, Sharrow SO, Rubin LA, Nelson DL, Rosenberg SA. *In vivo* administration of purified human interleukin-2 to patients with cancer: development of interleukin-2 receptor positive cells and circulating soluble interleukin-2 receptors following interleukin-2 administration. *Cancer Res* 1987, **47**, 2188–2195.
4. Rubin LA, Nelson DL. The soluble interleukin-2 receptor: biology, function and clinical application. *Ann Int Med* 1990, **113**, 619–627.
5. Hamblin TJ, Inzani V, Sadullah S, *et al.* A phase-II trial of recombinant interleukin-2 and 5-FU chemotherapy in patients with metastatic colorectal carcinoma. *Cancer Treat Rev* 1989, **16** (Suppl. 1), 163–167.
6. Poulton TA, Gallagher A, Potts RC, Swanson Beck J. Changes in activation markers and cell membrane receptors on human peripheral blood T lymphocytes during cell cycle progression after PHA stimulation. *Immunology* 1988, **64**, 419–425.