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Elevated serum levels of soluble interleukin-2 receptors in lung cancer and the effect of surgery

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Introduction

Activation of T lymphocytes leads to the expression of interleukin-2 receptors (IL-2R) on the cell surface (1) as well as the release of soluble IL-2R (sIL-2R) molecules into the circulation (2). T lymphocytes are the predominant IL-2R bearing cells (3) and hence serum sIL-2R level provides a satisfactory indicator of T-cell activation *in vivo*.

Elevated serum levels of sIL-2R have been reported in patients with small-cell lung cancer (4) (SCLC) and non-SCLC (5). Herein, we report a study designed to find out the sIL-2R concentrations in patients with non-SCLC and their changes following surgical resection.

Patients and Methods

Our sample population consisted of 59 consecutive patients with primary lung cancer (28 adenocarcinoma, 19 squamous cell carcinoma, four undifferentiated carcinoma and 8 SCLC).

Twenty-six patients had clinically operable non-SCLC and underwent surgical operation. However, only 13 patients (eight adenocarcinoma and five squamous cell carcinoma) had limited intrathoracic disease at operation and resection of tumour was performed. In 12 cases, extensive intrathoracic disease was found at operation including lymph nodes, superior vena cava and chest wall invasion and complete resection of tumour was not possible. One patient had complete resection of the lung tumour but was found to have brain metastasis 2 months after operation.

Eighteen patients with non-SCLC had distant metastasis detected on investigation and operation was not performed (ten adenocarcinoma, six squamous cell, two undifferentiated). The sites of metastasis included: four lymph node; three bone; five pleura; one brain; one pulmonary; one pericardium and three multiple sites. Seven patients had clinically localized disease but were inoperable because of poor lung function. Eight patients had SCLC and surgery was not considered.

Serum samples were taken from the patients before chemotherapy or surgical treatment was initiated. In patients with complete resection of tumour, serum samples were taken again at 3 weeks and 3 months after operation. Control serum samples were also taken from 41 normal healthy subjects. All serum samples were randomly assigned code numbers and assayed in a single batch without the knowledge of the clinical status of the patients, disease staging, tumour histology or treatment modality. Serum sIL-2R concentrations were measured by a modified ELISA method as previously described (6).

Results

The serum sIL-2R levels of the different groups of patients are shown in Fig. 1. The sIL-2R levels in the 59 patients with lung cancer were significantly higher than those in control subjects ($804{\cdot}4 \pm 63{\cdot}6$ U ml^{-1} *vs.* $374{\cdot}2 \pm 29{\cdot}9$ U ml^{-1}, $P < 0{\cdot}0001$). Similarly, the sIL-2R levels in 51 patients with non-SCLC ($782{\cdot}7 \pm 59{\cdot}9$ U ml^{-1}) and in eight patients with SCLC ($943{\cdot}2 \pm 283{\cdot}5$ U ml^{-1}) were significantly higher than those in control subjects ($P < 0{\cdot}0001$ and $P < 0{\cdot}02$ respectively). However, no significant difference was demonstrated between the sIL-2R levels in SCLC and non-SCLC ($P = 0{\cdot}79$).

The mean sIL-2R level in 18 patients with metastatic adenocarcinoma was $747{\cdot}9 \pm 79{\cdot}6$ U ml^{-1} which was not significantly different from that in eight subjects with resectable adenocarcinoma ($516{\cdot}4 \pm 71{\cdot}8$ U ml^{-1}, $P = 0{\cdot}14$). Similarly, the mean sIL-2R level in ten subjects with metastatic squamous-cell tumour was not significantly different from that in five subjects with resectable squamous cell lung cancer ($739{\cdot}9 \pm 62{\cdot}1$ U ml^{-1} *vs.* $704{\cdot}2 \pm 85{\cdot}4$ U ml^{-1}, $P = 0{\cdot}27$).

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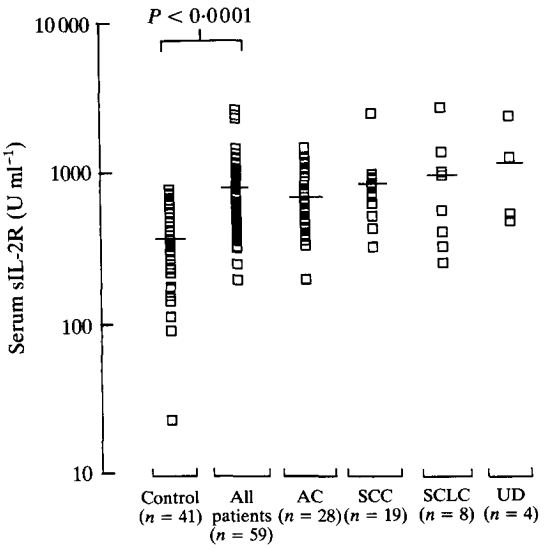

Fig. 1 Serum sIL-2R levels in patients with lung cancer and healthy controls. AC, adenocarcinoma; SCC, squamous-cell carcinoma; SCLC, small-cell lung cancer; UC, undifferentiated carcinoma.

Table 1 Serum sIL-2R levels in 12 patients with extensive intrathoracic disease and 13 patients with localized tumour detected at thoracotomy. AC, adenocarcinoma; SCC, squamous-cell carcinoma; UD, undifferentiated carcinoma

	Extensive disease*		Limited disease†	
	481	(AC)	883	(AC)
	837	(AC)	460	(AC)
	1053	(AC)	626	(AC)
	1478	(AC)	442	(AC)
	1254	(AC)	565	(AC)
	967	(AC)	595	(AC)
	759	(AC)	198	(AC)
	818	(SCC)	362	(AC)
	625	(SCC)	939	(SCC)
	725	(SCC)	853	(SCC)
	329	(SCC)	691	(SCC)
	2307	(UD)	721	(SCC)
			692	(SCC)
Mean	969·4		617·5	
(SEM)	(151·9)‡		(59·4)‡	

*$n = 12$, †$n = 13$, ‡$P = 0{\cdot}039$.

Twenty-six patients had undergone surgical operation. Twelve of them were found to have extensive intrathoracic disease at operation and their serum sIL-2R levels (Table 1) were significantly higher than those of 13 subjects with resectable tumour ($969{\cdot}4 \pm 151{\cdot}9$ *vs.* $617{\cdot}5 \pm 59{\cdot}4$ U ml^{-1}, $P = 0{\cdot}039$). If we take the normal range of sIL-2R as mean ± 2 SD of the normal control values, then nine of the twelve cases (75%) with extensive intrathoracic disease had sIL-2R levels above the upper limit of normal range. In contrast, in the 13 patients with resectable tumour, only four (31%) had marginally raised sIL-2R levels while the other nine cases had sIL-2R values within the normal range. There was one additional patient with adenocarcinoma resected but he had a cerebral metastasis detected 2 months later. His sIL-2R levels before and at 3 weeks after operation were 456 and 1799 U ml^{-1}, respectively.

In the 13 patients with tumour resected, one died at 6 weeks after operation from chest infection complicated with respiratory failure and another defaulted follow up. In the 11 remaining cases, there was no evidence of tumour relapse after 6–15 months follow up (mean 10 months). Their sIL-2R levels before operation ($598{\cdot}1 \pm 66{\cdot}8$ U ml^{-1}) was not significantly different from the levels at 3 weeks ($610{\cdot}7 \pm 60{\cdot}6$ U ml^{-1}) and 3 months ($532{\cdot}4 \pm 56{\cdot}7$ U ml^{-1}) after operation.

Discussion

In this study, we attempted to find out the serum sIL-2R levels in patients with non-SCLC, their relationship with the extent of disease and the changes following resection of the lung tumour. We found that serum sIL-2R levels were significantly higher in patients with non-SCLC compared to control subjects ($P < 0{\cdot}0001$). In patients with extensive intrathoracic disease detected at operation but without distant metastasis, their serum sIL-2R levels also appear to be higher than those with localized resectable tumour. However, there was no significant difference between the sIL-2R levels in those with metastatic disease compared to those with localized tumour.

For patients with the tumour resected, there was no significant difference between the pre- and post-operative serum sIL-2R levels up to 3 months after operation. However, one patient was found to have a rise in serum sIL-2R at 3 weeks which preceded the subsequent discovery of a cerebral metastasis at 2 months after operation. Therefore, elevation of serum sIL-2R level may occur during tumour relapse as in patients with nasopharyngeal carcinoma (7).

The source of sIL-2R in patients with non-SCLC may be the tumour itself or circulating activated T-cells (8). Previous studies on adenocarcinoma and squamous cell carcinoma have failed to demonstrate surface expression of IL-2R in these cell lines (5). Therefore activated T lymphocytes are probably the major source of sIL-2R in patients with non-SCLC. However, the exact role of the activated T lymphocytes and sIL-2R in patients with non-SCLC was uncertain.

Although we found that patients with extensive intrathoracic disease have higher serum sIL-2R levels, suggesting T-cell activation in these cases, the sIL-2R levels in those with distant metastasis were more variable. Some had very high levels while some had normal values, indicating a wide spectrum of T lymphocyte activity in patients with non-SCLC. The paucity of correlation between the extent of disease and serum sIL-2R level implies that there are probably multiple factors influencing the degree of T lymphocyte activation in addition to the tumour load. Other possible factors may include the immune status of the host, expression of antigen by the tumour cells and blood supply of the tumour which would affect the contact of T lymphocytes with antigen bearing tumour cells. Whether these different degrees of T-cell activation would affect the response to alternative treatment modalities like radiotherapy, chemotherapy or immunotherapy in patients with inoperable non-SCLC awaits further elucidation.

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