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The Biological Significance of Soluble Interleukin-2 Receptors in Solid Tumors

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Abstract—*In an attempt to further understand the biological significance of soluble IL-2 receptors (sIL-2R) in solid tumors, we have evaluated* 160 *cancer patients (breast*: 40; *lung*: 66; *colon*: 18; *stomach*: 22; *uterine cervix*: 14) *and* 58 *healthy subjects, as controls. Serum mean levels of sIL-2R, measured with an enzyme immunoassay, were significantly higher in cancer patients than in controls. Metastatic cancer patients showed significantly higher values than the non-metastatic ones; this difference was significant in all tumor histotypes, except small cell lung carcinoma. Moreover, in* 15 *patients in whom sIL-2R were evaluated either before or after radical surgery, a significant surgery-induced increase in sIL-R mean values was seen. Finally, the chemotherapy-induced rise in sIL-2R appeared to be associated with a lack of clinical response. These results seem to suggest that sIL-2R may be a marker of host biological response in patients with solid tumors, the significance of which needs further investigation.*

INTRODUCTION

A GREAT VARIETY of immune parameters, including CD4/CD8 ratio [1], interleukin-2 (IL-2) production [2] and LAK activity [3], has been proposed for monitoring host biological response in cancer patients in relation either to the clinical course of the neoplastic disease or to antitumor therapies. Moreover, it has recently been demonstrated that activated lymphocytes, in addition to the expression of IL-2 receptors on the cell surface, can release a soluble form of IL-2 receptors (sIL-2R) in the blood [4]. Abnormally high levels of sIL-2R have been described in both hemolymphopoietic neoplasms [5, 6] and solid tumors [7]. sIL-2R may be considered as a tumor marker in hemolymphopoietic tumors [5, 6], while the clinical significance of the increased concentrations of sIL-2R in solid neoplasms has still to be defined.

The present study was carried out to further analyze the circulating levels of sIL-2R in solid neoplasms in relation to the histotype of the tumor, clinical stage and response to therapy.

MATERIALS AND METHODS

The study included 160 patients of both sexes, with a median age of 53 years (range 32–71), affected by histologically proven solid neoplasms. All patients signed informed consent, and underwent uniform evaluation and staging. To investigate serum levels of sIL-2R, venous blood samples were drawn during the morning. No patient was under therapy with steroids or opioids during the present investigation. Patients under chemotherapy were evaluated at least 20 days from the last administration of cytotoxic drugs. To exclude possible interferences, patients with concomitant inflammatory diseases were not included in the study. Breast cancer (n = 40), lung cancer (n = 66; non-small cell: 46; small cell: 20), colorectal cancer (n = 18), gastric cancer (n = 22) and uterine cervix carcinoma (n = 14) were the neoplasms observed in our patients. Seventy-nine patients had locally limited disease, while the other 81 showed distant organ metastases; the diagnosis of locally limited disease was made on the basis of normality at chest radiogram, abdominal echography, CT brain scan and bone scintigraphy. Ninety-three patients were untreated, whereas the other 67 had been previously treated with surgery and/or radiotherapy and/or chemotherapy. As controls, 58 sex- and age-matched healthy subjects were included in the study; controls were chosen among the laboratory and nursing staff and blood donors at a local transfusion center.

In addition, 15 patients with operable cancer were evaluated either before or 10 days after radical surgery (breast: four; lung: five; colon: three; sto-

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mach: three). Finally, 20 patients (breast: nine; lung: nine; stomach: two) with advanced disease were studied either before, or at least 20 days after, the last chemotherapeutic cycle; tumor histotype was ductal carcinoma for breast cancer, epidermoid carcinoma for lung cancer, and adenocarcinoma for gastric cancer.

sIL-2R serum levels were measured with a sandwich enzyme immunoassay using commercial kits (T Cell Sciences, Cambridge, MA), according to the method previously described by Rubin *et al.* [4]. sIL-2R concentrations were expressed in units/ml. The sensitivity of the assay was 50 U/ml. Intraassay and interassay coefficients of variation were 4% and 11%, respectively. In our laboratory, sIL-2R serum levels were considered to be within the normal range when they were less than 480 U/ml (95% confidence limits). Data were reported as mean ± S.E., and analyzed by Student's *t* test.

RESULTS

The mean levels of sIL-2R observed in healthy subjects and in cancer patients are listed in Table 1. The mean serum values of sIL-2R were significantly higher in cancer patients than in controls ($P < 0.001$). Metastatic cancer patients showed significantly higher mean levels of sIL-2R than those without metastases ($P < 0.001$). In the only case of small cell lung cancer, there was no significant difference between metastatic and non-metastatic patients, whereas in all other tumor histotypes metastatic patients had statistically higher mean values of sIL-2R than those with locally limited disease (breast cancer: $P < 0.005$; non-small cell lung cancer: $P < 0.005$; colorectal cancer: $P < 0.05$; gastric cancer: $P < 0.05$; cervix carcinoma: $P < 0.025$). No significant difference, however, was seen in relation to tumor histotype.

An increase of sIL-2R greater than 100% was seen after radical surgery in 9/15 (60%) cancer patients, and they became above the normal range in 14//15 (93%) patients, while before surgery they were abnormally elevated in 6/15 (40%) patients only. sIL-2R mean values were significantly higher after than before radical surgery ($P < 0.005$) (see Table 2).

Within the chemotherapy group, sIL-2R mean levels observed at the end of chemotherapy were significantly higher ($P < 0.001$) in progressed patients than in the responder ones, while no difference was seen before chemotherapy. The type of chemotherapy and sIL-2R values are reported in Table 3.

DISCUSSION

The results of this study, by showing significantly higher levels of sIL-2R in patients with metastatic solid tumor than in those with limited disease, would suggest that tumor dissemination may be associated with an increased release of sIL-2R in the blood. Besides, this study suggests that radical

Table 1. *Serum levels of sIL-2R (mean ± S.E.) in healthy subjects and in cancer patients*

Cases	*n*	sIL-2R (U/ml)	Percentage of high sIL-2R
Healthy subjects	58	278 ± 13	0
Cancer patients	160	796 ± 46	99/160 (61.9%)
LLD	79	482 ± 21	33/79 (41.8%)
MD	81	1116 ± 73	66/81 (81.5%)
Breast cancer	40	760 ± 72	21/40 (52.5%)
LLD	18	358 ± 52	5/18 (27.8%)
MD	22	961 ± 131	16/22 (72.7%)
Non-small cell lung cancer	46	1003 ± 129	31/46 (67.4%)
LLD	20	506 ± 52	9/20 (45.0%)
MD	26	1255 ± 171	22/26 (84.6%)
Small cell lung cancer	20	834 ± 136	18/20 (90.0%)
LLD	11	627 ± 67	9/11 (81.8%)
MD	9	949 ± 251	9/9 (100.0%)
Colorectal cancer	18	863 ± 159	10/18 (55.6%)
LLD	10	524 ± 65	4/10 (40.0%)
MD	8	1288 ± 287	6/8 (75.0%)
Gastric cancer	22	810 ± 137	12/22 (54.5%)
LLD	12	496 ± 32	4/12 (33.0%)
MD	10	1124 ± 249	8/10 (80.0%)
Uterine cervix carcinoma	14	776 ± 152	7/14 (50.0%)
LLD	8	473 ± 51	2/8 (25.0%)
MD	6	1179 ± 238	5/6 (83.3%)

*LLD: locally limited disease; MD: metastatic disease.

Table 2. Individual and mean serum levels of sIL-2R in 15 cancer patients before and 10 days after radical surgery

Patient	Tumor	sIL-2R (U/ml) Before	After
1	Breast	270	1405
2	Breast	462	935
3	Breast	287	335
4	Stomach	610	1387
5	Lung	587	665
6	Breast	395	610
7	Stomach	625	1272
8	Colon	301	936
9	Colon	406	851
10	Lung	905	1421
11	Stomach	391	676
12	Lung	434	1037
13	Lung	548	733
14	Lung	373	757
15	Colon	644	1315
$\bar{x} \pm$ S.E.		482 ± 44	956 ± 87

surgery for solid tumor may be followed by a remarkable increase in sIL-2R blood concentrations. Finally, the present investigation seems to suggest that clinical response to chemotherapy may be associated with a normalization of sIL-2R serum levels, while a further increase would characterize cancer patients, who progressed under chemotherapy; however, the insufficient number of cases and the different chemotherapeutic regimens do not allow us to draw definite conclusions about the relationship between changes in sIL-2R levels and response to chemotherapy, even though, at present, there is no evidence that the type of therapy and of histology may have any impact on sIL-2R release.

The mechanisms responsible for the enhanced production of sIL-2R in metastatic solid tumors are still obscure, and at present it is not possible to establish if it is simply due to an activation of the immune system, induced by tumor growth, or if it is the expression of an immune dysfunction, which could play a role in the neoplastic progression. In the same way, it remains to be established if changes in sIL-2R concentrations in relation to radical surgery and chemotherapy may depend upon variations of host–tumor interaction. However, because of the documented ability of sIL-2R to bind IL-2 [8], their increased production might cause a competition for IL-2 with IL-2 cell surface receptors, and reduce the availability of IL-2 for IL-2-dependent immune functions. However, it was beyond the aim of the present study to analyze the

Table 3. Individual and mean serum levels of sIL-2R in 20 cancer patients before and after chemotherapy, and their relation to clinical response

Patient	Tumor	Chemotherapy*	Clinical response†	sIL-2R (U/ml) Before	After
1	Breast	EPI	PD	948	1421
2	Breast	CMF	PD	539	935
3	Lung (NSC‡)	PM	PD	1093	1377
4	Lung (SC‡)	CEV	PR	603	408
5	Lung (SC‡)	CEV	PD	636	841
6	Breast	FEC	PD	1092	2312
7	Lung (NSC‡)	PM	PD	423	876
8	Lung (NSC‡)	PM	PD	744	1124
9	Breast	CMF	PD	448	1026
10	Breast	EPI	PD	454	936
11	Stomach	5-FU	PR	2360	815
12	Lung (SC‡)	CEV	CR	638	406
13	Stomach	5-FU	PD	596	1214
14	Breast	FEC	PR	741	485
15	Lung (SC‡)	CEV	PD	702	1863
16	Lung (NSC‡)	PE	PR	848	245
17	Lung (SC‡)	ECEP	PR	703	524
18	Breast	CMF	PR	1109	639
19	Breast	FEC	PD	1023	1564
20	Breast	CMF	PD	914	1556
	$\bar{x} \pm$ S.E.	Responder patients (n = 7)		857 ± 107	503 ± 71
		Progressed patients (n = 13)		739 ± 69	1313 ± 122

*EPI: epirubicin; CMF: cyclophosphamide, methotrexate, fluorouracil; CEV: cyclophosphamide, epirubicin, vincristine; FEC: fluorouracil, epirubicin, cyclophosphamide; PM: cisplatin, mitoxantrone; 5-FU: fluorouracil; PE: cisplatin, etoposide; ECEP: epirubicin, cyclophosphamide, etoposide, cisplatin.

†CR: complete response; PR: partial response; PD: progressive disease.

‡NSC: non-small cell; SC: small cell.

affinity of sIL-2R in relation to that of the cell surface IL-2 receptor.

Successive studies will be required to further understand the biological and prognostic significance of sIL-2R in solid neoplasms. These studies will involve the evaluation of sIL-2R during the clinical course of the neoplastic disease and the investigation of the *in vitro* effects of sIL-2R on IL-2-dependent immune reactions.

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