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SERUM SOLUBLE INTERLEUKIN-2 RECEPTOR IN COLORECTAL CANCER

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Preoperative serum soluble interleukin-2 receptor (IL-2R) levels were measured in patients with colorectal cancer, and correlated with various factors as stage, lymph node metastasis, liver metastasis, grade, serum CEA and IAP (immunosuppressive acidic protein). The levels of serum soluble IL-2R in Dukes stage C were significantly higher than in normal control and in Dukes stage A. Serum levels were also significantly higher in patients with lymph node metastasis than in patients without such metastasis, and in IAP positive patients compared to IAP negative patients. Preoperative serum IL-2R levels thus seem to reflect the stage of the disease.

Recent studies have provided evidence of a provocational role of cytokines in diverse diseases. Interleukin-2 (IL-2) thus plays an integral role in the activation of T-lymphocytes and host antitumor immune response. It is known that soluble interleukin-2 receptor (IL-2R) is released from its specific membrane receptor on activated T lymphocytes and detected in the peripheral blood stream as a form of the α-chain of IL-2R. Increased levels of serum soluble IL-2R have been found in patients with various diseases including leukemia, lung cancer, sarcoidosis, viral infections, and autoimmune diseases. However, there are few papers on serum soluble IL-2R levels in patients with cancers of the digestive tract. Therefore, we measured the serum soluble IL-2R level in patients with colorectal cancer and studied its relationship with stage, lymph node metastasis, tumor size, histological grade, and tumor markers, such as CEA (carcinoembryonic antigen) and IAP (immunosuppressive acidic protein).

Material and Methods

Thirty patients (15 males and 15 females) aged between 29 and 88 admitted to our hospital from February 1992 to March 1993 were included in the study. The tumours were staged according to Dukes classification (1). In all but one patient, the tumor was resected with either a curative (24/30) or a non-curative (5/30) procedure. The blood samples were collected before surgery and stored at −80°C until later analysis. The normal control group for serum soluble IL-2R comprised 14 individuals (healthy hospital personnel).

Serum soluble IL-2R was measured by an enzyme-linked immunosorbent assay using cell-free interleukin-2 receptor kits (Yamanouchi Pharm. Co., Tokyo, Japan), according to the manufacturer's instructions. Briefly, the serum samples were treated with a monoclonal antibody that recognized one epitope of human soluble IL-2R. After 2 h of incubation and washing, horse-radish peroxidase-conjugated monoclonal antibody directed to a second epitope was added. This binded to the IL-2R captured by the first monoclonal antibody. The color reaction was terminated by addition of 2N H_2SO_4 and absorbance was measured at 490 nm. Serum IAP levels were measured by turbidimetry immunoassay (TIA), using human anti-IAP serum purchased from Sanko Pharm. Co., Japan. An IAP value of less than 500 μg/ml was considered normal.

The results are expressed as a mean ± standard error of the mean. The data were analyzed with Student's t-test and linear correlation coefficient. A p-value below 0.05 was considered to be significant.

Results

Concerning the preoperative levels of serum soluble IL-2R, there was no significant difference between male

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Table 1

Serum soluble IL-2R levels in normal subjects and in patients with colorectal cancer. a, b vs c; statistically significant ($p < 0.05$), a vs. b: statistically not significant

	n	Mean ± s.e.m. (U/ml)
Normal controls	14	481 ± 36[a]
Dukes A	12	443 ± 47[b]
Dukes B	3	614 ± 158
Dukes C	15	917 ± 237[c]

and female patients with colorectal cancer (777 ± 229 versus 699 ± 125 U/ml respectively) or between patients with colonic (14/30) and rectal cancer (16/30) (728 ± 221 versus 746 ± 150 U/ml respectively).

Patients with Dukes stage C had significantly higher serum soluble IL-2R values than the normal control group and patients of Dukes stage A ($p < 0.05$) (Table 1). Patients with lymph node metastasis had significantly higher levels than patients without such metastasis ($p < 0.05$) (Table 2). Patients with liver metastasis had slightly higher values compared to patients without such metastasis but this difference was not statistically significant (Table 2). There was also a significant difference between patients with and without histological venous invasion ($p < 0.05$), whereas no significant difference was found between groups stratified according to grade or to histological lymphatic invasion (Table 3).

Table 2

Serum soluble IL-2R levels in patients with or without lymph node metastasis, and with or without liver metastasis. a vs b: statistically significant ($p < 0.05$)

	n	Mean ± s.e.m. (U/ml)
Lymph node metastasis	−15	477 ± 49[a]
	+15	998 ± 236[b]
Liver metastasis	−26	642 ± 99
	+ 4	1 344 ± 722

Table 3

Serum soluble IL-2R levels in each group, classified by histopathological findings (pathological grade, lymphatic invasion, and venous invasion). a vs b: statistically significant ($p < 0.05$)

	n	Mean ± s.e.m. (U/ml)
Well differentiated	9	980 ± 310
Moderate differentiated	19	657 ± 137
Poorly differentiated	1	606
Mucinous	1	226
Lymphatic invasion	−3	422 ± 67
	+26	714 ± 133
Venous invasion	−9	410 ± 48[a]
	+20	807 ± 166[b]

Table 4

Serum soluble IL-2R levels in patients, grouped by the positive or negative cases of tumor markers (CEA and IAP). a vs b: statistically significant ($p < 0.05$)

	n	Mean ± s.e.m. (U/ml)
CEA	−15	556 ± 99
	+13	753 ± 242
IAP	−12	434 ± 45[a]
	+16	972 ± 229[b]

There was no significant difference between the CEA positive and CEA negative groups, whereas the levels in the IAP positive patients were significantly higher than in the IAP negative ones ($p < 0.05$) (Table 4). No significant correlation was found between preoperative serum soluble IL-2R level and tumor size (maximum diameter) (Figure).

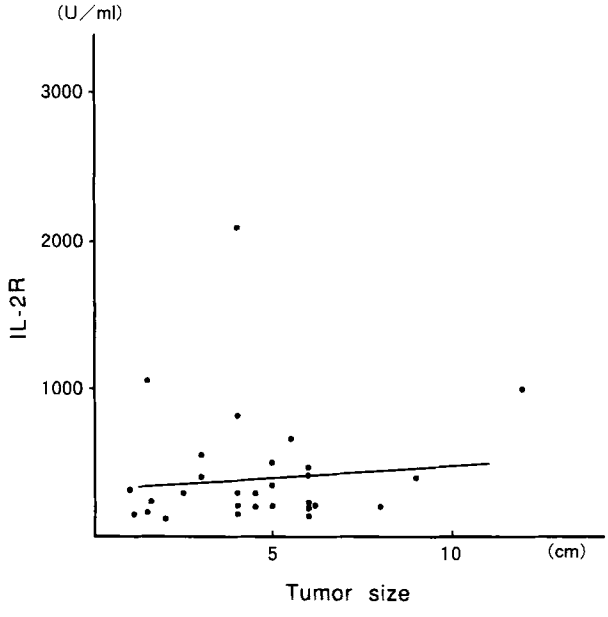

Figure. Correlation between serum soluble IL-2R level and size of the tumor ($r = 0.04$, $p = NS$).

Discussion

At present, it is known that interleukin-2 (IL-2) is one of the main cytokines that regulate the immune responses (2). IL-2 activates T-lymphocytes, whose membrane-bound receptors have high affinity to IL-2. T-lymphocytes activated by IL-2 release a soluble form of interleukin-2 receptor (IL-2R) to the blood (3). High levels of soluble IL-2R have been observed in patients with various autoimmune disorders (4), malignant disease (5–10) and viral infections (11).

Very little has been reported on serum soluble IL-2R levels in colorectal cancer (12–14). Lissoni et al. (12) found in a material of 18 cases that patients with metastasis had statistically higher mean values of serum soluble IL-2R than those with locally limited disease. Our study also showed significantly higher levels of serum soluble IL-2R in patients with lymph node metastasis than in those without such metastasis. In our study, however, there was statistically no difference between patients with and without liver metastasis. One could therefore speculate that T-lymphcytes in regional lymph nodes are stimulated by metastatic cancer cells to produce large amounts of IL-2R which could explain the high levels of serum soluble IL-2R in the peripheral blood. Inagaki et al. (15) reported that staining for IL-2R antibody demonstrated an aggregation of IL-2R positive cells around metastasis from gastric cancer in the regional lymph nodes. Further studies are needed to elucidate these phenomena.

In our study, the serum soluble IL-2R levels were significantly associated with histological venous invasion but not with grade. There was also a tendency towards higher levels in patients with histological lymphatic invasion but this difference was not statistically significant. One might speculate, however, whether the production of IL-2R in T-lymphocytes is stimulated by venous and lymphatic invasion but not by the histological grade.

The serum levels of soluble IL-2R were significantly higher in IAP-positive than in IAP-negative patients. IAP is one of the acute phase proteins first detected in ascitic fluid of patients with gastric cancer (16). It is produced by lymphocytes and macrophages and has various immunosuppressive effects. In particular, IAP production is induced by immune complexes which attach themselves to lymphocytes and macrophages, resulting in a high serum titer of IAP in patients with malignant tumors (17, 18). The observed increases of IAP and serum soluble IL-2R in our patients may be parallel phenomena or expression of some type of interaction.

There was no correlation between the serum IL-2R level and the size of the tumor. From these data, it seems conceivable that an enlargement of the tumor in itself does not induce an increment of the immunological status in colorectal cancer, especially as far as T-lymphocytes are concerned.

We conclude that the preoperative serum IL-2R level in patients with colorectal cancer reflects the stage of disease and that it seems especially correlated to the occurrence of lymph node metastasis.

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