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Serum level of soluble interleukin-2 receptor α correlates with the clinical course and activity of Wilms' tumour and soft tissue sarcomas in children

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Abstract
Wilms' tumour (WT) and soft tissue sarcomas (SA) in children lack reliable biochemical markers. This study was carried out to determine the clinical significance of serum soluble interleukin-2 receptor α (sIL-2Rα) in the diagnostics and treatment monitoring of children with WT and SA. The study included 48 children: ten with WT, eight with SA and 30 healthy controls. The sIL-2Rα levels (ELISA) and rates of elevated sIL-2Rα values were estimated prospectively at diagnosis and in complete remission during treatment and after therapy. As the dependence on age was determined, the levels of sIL-2Rα were expressed as multiplications of the upper value of the normal range for a particular age ($\times$N). Median pretreatment levels of sIL-2Rα in patients exceeded those of healthy controls (1.79 $\times$N for WT and 1.53 for SA vs. 0.61 for controls; $p < 0.001$) as did the rates of elevated sIL-2Rα values (80% of WT and 87.5% of SA patients vs. 0% of controls). Good response to therapy was paralleled by a significant decline of pretreatment sIL-2Rα levels and its elevated rates. Thus, sIL-2Rα determination may be of some value in the diagnostics and treatment monitoring of childhood WT and SA.

Keywords: *Soluble interleukin-2 receptor α, diagnostics, treatment monitoring, Wilms' tumour, soft tissue sarcomas, children*

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Introduction

Since Morgan et al. reported in 1976 that interleukin-2 (IL-2) is a T-cell growth factor, IL-2 has been investigated and characterised as one of the most important interleukins in the regulation of the immune system (Morgan et al. 1976). It plays an essential role in a great number of anti-tumour reactions, stimulating the proliferation and function of T, B and natural killer (NK) cells as well as other cytotoxic effector cells. To exert its biological effect, IL-2 must interact with its specific receptor (IL-2R) expressed on the cell membrane of activated T and B lymphocytes and monocytes (Armitage et al. 1986, Kawashima et al. 2000, Sondel 1997). The cell surface-bound IL-2R is composed of at least three distinct subunits called α (55 kDa), β (75 kDa) and γ (64 kDa) chains. Each subunit is able to bind the ligand independently with

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either low (IL-2Rα) or intermediate (IL-2Rβ and γ) affinity (Honda et al. 1990, Sondel 1997). It has been shown that the high-affinity receptor for IL-2 consists of all three subunits combined non-covalently and the presence of the α chain is necessary for the high-affinity IL-2R formation (Gutgsell & Malek 1994). Although resting as well as mature activated lymphocytes constitutively express the β and γ chains, the α chain (also termed Tac molecule) is rapidly induced and expressed only after activation of mononuclear cells (Djeu et al. 1993, Espinoza-Delgado et al. 1990, Sugamura et al. 1990).

In 1985, Rubin et al. reported that the soluble form of the α subunit of IL-2R (sIL-2Rα) was released spontaneously in the culture supernatants of *in vitro* cultured T cells after stimulation with lectins and mitogens. The authors have proven that the soluble form of the α chain is smaller than its membrane counterpart (45 kDa vs. 55 kDa), but it retains the ability to bind IL-2 efficiently (Rubin et al. 1986, Rubin & Nelson 1990). An enzyme-linked immunosorbent assay (ELISA) with the use of two non-competitive murine antihuman IL-2Rα antibodies (anti-Tac and 7G7/B6) has enabled detection and quantification of the released soluble form of the Tac molecule (sIL-2Rα) (Waldmann et al. 1992).

Soluble IL-2Rα has been found in the serum and other body fluids of healthy individuals and its level reflects the activation of innate immunological responses occurring under physiological stimuli (Rubin et al. 1985, Rubin & Nelson 1990). Increased serum levels of sIL-2Rα have been found in a variety of autoimmune, inflammatory and infectious diseases as well as in acquired immunodeficiency disorders (Naveau et al. 1999, Peteiro-Cartelle & Alvarez-Jorge 1999, Shi et al. 1999). Highly increased sIL-2Rα levels have been reported at diagnosis of the majority of lymphoproliferative disorders, including hairy cell leukaemia (HCL), adult T-cell leukaemia (ATL), Hodgkin's and non-Hodgkin's lymphomas (HL, NHL), chronic myeloid leukaemia (CML), chronic lymphoblastic leukaemia (CLL) and others (Chilosi et al. 1987, Janik et al. 2004, Marcon et al. 1988, Moon et al. 2004, Nakase et al. 2005, Stasi et al. 1994, Viviani et al. 1998). It is suggested that in these haematological conditions, sIL-2Rα is directly released by the neoplastic cells and thus reflects the tumour burden and disease activity. However, in most malignant solid tumours, inflammatory and autoimmune diseases, elevated levels of sIL-2Rα are likely to be the product of normal peripheral mononuclear cells activated in response to the neoplasm's development and growth (Murakami 2004). Nevertheless, the pretreatment serum levels of sIL-2Rα have been shown to reflect the activity, advancement and biological aggressiveness of most neoplasms in adults, as well as correlating with prognosis and overall survival.

Neoplastic disease of childhood comprises a broad spectrum of malignant disorders characterised by multiple histopathological, clinical and biological features, very different from those in adults. Reports concerning the significance of serum sIL-2Rα determination in paediatric malignancies are not numerous and concentrate predominantly on its level at diagnosis before treatment administration (Bodey et al. 1996, Pui et al. 1987, Pui et al. 1988, 1989, 1993). To the best of our knowledge there have been only two publications considering the role of sIL-2Rα in children affected by malignant solid tumours. Furthermore, no reports exist on the clinical usefulness of serial measurements of sIL-2Rα during anti-tumour therapy in childhood solid malignancies.

Thus, the aim of the present study was to evaluate whether serum levels of soluble interleukin-2 receptor correlate with the clinical course and response to therapy in children affected with two common types of paediatric solid neoplasms: nephroblastoma (Wilms' tumour) and soft tissue sarcomas. These tumour types lack any specific biochemical marker able to supplement the diagnostic and prognostic methods used in everyday oncological practice.

Material and methods

The study included 18 children with malignant solid neoplasms, treated in the Division of Haematology and Oncology of the Department of Paediatrics, Haematology, Oncology and Endocrinology, Medical University of Gdansk, Poland, during 1995–2000. The group covered two distinct histological types of childhood malignancies, i.e. Wilms' tumour (WT, ten patients) and soft tissue sarcomas (SA, eight patients). The diagnosis, staging, treatment and assessment of response to therapy were carried out in full accordance with schemes provided by the International Society of Paediatric Oncology (SIOP) and Polish Paediatric Solid Tumours Study Groups for each type of neoplasm. Pathological examinations were verified in two distinct institutions. The control group consisted of 30 healthy children in whom no inflammatory or infectious diseases had been reported during the previous 3 months. The clinical characteristics of the patients and controls are shown in Table I.

In the cancer patients, serum levels of sIL-2Rα were determined in a prospective manner at particular stages of disease: before treatment (at diagnosis), in complete clinical remission (CR) during treatment, and after successful termination of therapy. The determination of sIL-2Rα was carried out both for the whole malignant solid tumours group and separately for the WT and SA patients. Also, the rates of elevated sIL-2Rα measurements were estimated for the whole oncological group, for each subgroup separately and for each phase of disease course. Serum sIL-2Rα levels were evaluated once in the children in the control group, after informed consent by the parents.

Table I. Clinical characteristics of patients affected with solid malignancies and controls.

	Wilms tumour	Soft tissue sarcomas	Control group
Number of patients	10	8	30
Age (years):			
Range	0.9–10.6	0.3–13.1	2.3–16.6
Median	4.2	5.7	8.8
Sex (F/M)	7/3	6/2	15/15
Primary tumour localisation	left kidney – 6 right kidney – 4	minor pelvis – 3 limbs – 2 head/neck – 2 orbit – 1	Completely healthy children with no previous or actual infection
Histology			
Favourable	2	2	–
Unfavourable	8	6	–
Stage at presentation			
I+II	4	2	–
III+IV	6	6	–

The study was approved by the Local Ethical Committee (decision no. 367/95).

Soluble serum IL-2Rα assay

Blood collected from patients and controls was centrifuged at 2000 rpm for 15 min to separate the serum. Serum samples were stored frozen at −70°C until assayed. Measurements of sIL-2Rα levels were performed in duplicate by the commercially available enzyme-linked immunosorbent assay (ELISA, Dako, Heverlee, Belgium). To avoid the possible influence of immunological activation caused by factors other than malignancy on serum sIL-2Rα determinations, the blood samples during oncological treatment were collected with respect to strict rules. All the serum sIL-2Rα measurements during therapy were performed in patients with no clinical signs of actual or previous (at least 14 days before) infectious or inflammatory disorder. Blood samples were collected at least 30 days after termination of radiotherapy, general anaesthesia and surgical procedure and at least 14 days after stopping the haematopoietic growth factor (granulocyte colony stimulation factor, G-CSF) administration. In addition, to exclude the influence of renal impairment on serum levels of sIL-2Rα, serum blood urea nitrogen (BUN) and creatinine level were checked. They appeared to be normal in all patients and controls at the time of sample collection. Children included in the control group were examined for actual and previous infectious conditions, as well as impairment of other body organs. The blood count, renal and liver function tests, as well as the erythrocyte sedimentation rate (ESR) and C-reactive protein concentration, were within normal range in all children in the control group.

Statistical analysis

The results were subjected to statistical analysis using the computer programmes: *Statistica 5.0* and *S-PLUS*. Correlation of serum sIL-2Rα with the age of the children in the control group was analysed using the non-parametric Spearman test. Once the dependence of sIL-2Rα level on age had been determined (correlation factor $R = 0.54$, $p = 0.002$), the values from the receptor analysis were expressed as a multiplication of the upper limit of the normal range (95% confidence interval for residual values) assessed for a particular age. To eliminate the influence of age on IL-2Rα levels obtained in oncological patients, the values of the receptor analysis were presented as 'xN' (where N indicates the value of the upper limit of the normal range for a particular age). After ascertainment of the data distribution using the Kolmogorov–Smirnov test, all results of sIL-2Rα determinations were subjected to statistical analysis using non-parametric tests (Mann–Whitney U test, Wilcoxon's Matched Pairs Test, Sign Test). All p values less than 0. 05 were considered to be statistically significant.

Table II. Serum sIL-2Rα levels in cancer patients at different stages of disease in comparison to healthy controls.

Levels of sIL-2Rα (xN) at different phases of disease	Wilms tumour	Soft tissue sarcomas	Solid tumours together	Control group
At presentation (*n*)	10	8	18	30
Range	0.87–8.65	0.95–4.98	0.87–8.65	0.18–1.06
Median	1.79*†‡	1.53*†‡	1.59*†‡	0.61
% of elevated values	80%	87.5%	83.3%	0%
CR during therapy (*n*)	7	5	12	
Range	0.66–2.58	0.35–2.39	0.35–2.58	
Median	1.39**	0.95**	1.06**	
% of elevated values	57%	14%	35.7%	
CR after treatment (*n*)	5	3	8	
Range	0.60–3.93	0.60–0.98	0.60–3.93	
Median	1.12**	0.61**	0.82**	
% of elevated values	43%	10%	29.2%	

CR, complete remission.
*$p < 0.001$ compared to healthy controls, **$p < 0.05$ compared to measurements at presentation, †$p < 0.05$ compared to CR during therapy, ‡$p < 0.05$ compared to CR after treatment.

Results

Correlation of serum sIL-2Rα with age

Analysis of serum sIL-2Rα levels in healthy children in the control group proved their dependence on age (correlation factor $R = 0.54$, $p = 0.002$). Thus, the levels of IL-2Rα obtained in oncological patients were expressed as a multiplication of upper value of normal range assessed for a particular age. This was presented as ' ×N'.

Levels of sIL-2Rα and rates of elevated values at neoplasm diagnosis

Serum sIL-2Rα levels for cancer patients at diagnosis and for the controls are reported in Table II. The median pretreatment level of sIL-2Rα determined for the whole oncological group was significantly elevated when compared with healthy children ($p < 0.001$). Similarly, when analysed separately in two distinct histological types of neoplasms, serum sIL-2Rα levels proved to be significantly higher in both WT and SA patients compared with the control group ($p < 0.001$). The rates of elevated initial values of Tac antigen for the whole group of cancer patients, as well as for children with WT and SA, were 83.3%, 80% and 87.5%, respectively. In the healthy children from the control group, no levels of sIL-2Rα exceeding the upper limit of the normal range for a particular age were found.

Levels of sIL-2Rα and rates of elevated values at different stages of neoplastic disease

The sIL-2Rα levels in children with solid neoplasms at different stages of disease are shown in Table II. It was observed that sIL-2Rα values determined for the whole oncological group at all stages of anti-tumour treatment were significantly elevated when compared with the median level determined in the healthy controls. The median

level of sIL-2Rα at diagnosis significantly exceeded the level observed in the phase of complete CR, both during treatment and after stopping therapy ($p < 0.05$). It was shown that, in parallel with the attainment of CR of the cancer, the level of sIL-2Rα decreased considerably; however, it still remained higher than in children from the control group ($p < 0.05$). Also, the rates of elevated sIL-2Rα values determined for particular phases of neoplastic disease seemed to reflect its course and activity. High rates of increased sIL-2Rα measurements were reported at diagnosis (83.3%), while in CR, during and after termination of therapy, they decreased to 35.7% and 29.1%, respectively. Both the median level of sIL-2Rα and the rate of sIL-2Rα elevated values determined in the CR phase of disease, even after treatment, did not return to the normal range.

Discussion and conclusions

To the best of our knowledge, the study presented here is the first one to demonstrate the clinical use of serial measurements of serum sIL-2Rα during oncological therapy of children with WT and SA.

In our report, the pretreatment serum levels of sIL-2Rα in 18 children with the above-mentioned malignant solid neoplasms were significantly elevated when compared with healthy children ($p < 0.001$). This phenomenon was found in both the whole oncological group and in two distinct histological subtypes of neoplasms, including WT and SA. Similarly, the rates of elevated initial values of Tac antigen for the whole group of cancer patients, as well as for WT and SA patients separately, exceeded significantly those of the controls, comprising the great majority of cases in each cancer type (80% and 87. 5%, respectively).

Several studies have shown that serum levels of sIL-2Rα increase significantly, especially in the active pretreatment phase of the malignant disease. The highest reported levels of serum sIL-2Rα have been reported in adult patients with leukaemia (up to 69 000 U ml^{-1} in ATL and 48 000 U ml^{-1} in HCL) and aggressive non-Hodgkin's lymphomas (Chilosi et al. 1987, Marcon et al. 1988, Stasi et al. 1994, Wakao et al. 2002). These levels were suggested to reflect directly the burden of the malignant transformed cells, expressing constitutively Tac antigen on their surface.

Adult patients with particular histological types of malignant solid tumours (including malignant melanoma and carcinomas of the lungs, kidney, pancreas, stomach, colon, ovaries and liver) have been reported recently to exhibit high levels of serum sIL-2Rα at presentation, especially when diagnosed in advanced stages (Boyano et al. 1997, Brunetti et al. 1999, Izzo et al. 1999, Kallio et al. 2001, Kawashima et al. 2000, Murakami et al. 2002, Rutkowski et al. 2002, Sakata et al. 2002, Sedlaczek et al. 2002). Since the expression of IL-2Rα has been reported in the cell lines of only some histological types of malignant solid neoplasms (Tartour et al. 2001, Wang et al. 2000), it has been suggested that elevated sIL-2Rα levels in the body fluids of patients with solid tumours reflect the augmented release of this receptor from normal lymphoid cells activated in response to tumour growth. However, most authors postulate that increased levels of sIL-2Rα do not originate from activated peripheral blood mononuclear cells, but most probably are released from activated lymphoid cells infiltrating neoplastic tissues (Sakata et al. 2002, Sharma et al. 1991, Tartour et al. 2001, Trentin et al. 1994).

In paediatric series, elevated serum levels of sIL-2Rα have been reported at diagnosis in children affected mostly with lymphoproliferative disorders, including ALL, NHL, HL and haemophagocytic histiocytic syndrome (Pui et al. 1987, 1988, 1989, 1993, Komp et al. 1988, 1989). Haemophagocytic histiocytic syndrome appeared to be associated with extremely high levels of marker, ranging from 23 600 to 75 200 U ml^{-1}, as reported by Komp et al. (1989). These authors were the first to show that serum sIL-2Rα levels in healthy children were much higher than in adults and that they changed significantly with age, with highest levels observed in infants and young children. Based on the sIL-2Rα measurements in sera of 122 healthy children aged from 0 (umbilical blood) to 15 years Komp et al. (1988) estimated the reference ranges for sIL-2Rα in particular age series. Our study confirmed the findings of Komp et al., as we were also able to demonstrate the correlation of serum sIL-2Rα levels with age in 30 healthy children included in the control group (correlation factor $R = 0.54$, $p = 0.002$, data not shown).

This observation is of great clinical importance as it indicates the necessity to create an age-adjusted control group, or to express each sIL-2Rα value obtained in the study as a multiplication of the upper limit of the reference range assessed for a particular age of the patient. The latter method was implemented in our study to avoid the influence of age on the IL-2Rα levels found in oncological patients. Using this method of presenting results, we found no sIL-2Rα values exceeding the reference ranges established for age in healthy children in the control group.

Elevated pretreatment sIL-2Rα levels were reported in the study on paediatric solid tumours by Bodey et al. (1996). The authors stated that sIL-2Rα determination was of significant value not only in diagnostics but also in overall survival prediction. However, Pui et al. found no correlation of the initial sIL-2Rα values and disease stage in children with WT, SA and bone sarcomas (Pui et al. 1985).

In addition to making an early and correct diagnosis, it is optimal for the oncologist to monitor the effects of anti-tumour therapy. The clinical usefulness of serial measurements of serum sIL-2Rα levels in children with malignant solid tumours has not been assessed to date. Thus, in our study we tried to clarify this issue in a group of 18 children with WT and SA. It was shown that a good response to anti-tumour therapy was paralleled by the significant decline of pretreatment sIL-2Rα levels (Table II, Figure 1). The median value of the receptor determined in a phase of complete remission of disease was significantly lower than before therapy; however, it still remained higher than in the children in the control group. Also, the rates of elevated sIL-2Rα values decreased significantly with ongoing treatment and with attainment of complete remission.

Literature studies on the role of sIL-2Rα in the monitoring of therapy in patients with solid malignancies are not numerous and predominantly consider adult patients. In the report of Vonderheid et al. (1998) 36 patients with advanced cutaneous T-cell lymphoma underwent serial measurements of sIL-2Rα levels during treatment with extracorporeal photopheresis and other modalities. The concentration of serum sIL-2Rα correlated well with the disease status and was found more useful than lactate dehydrogenase concentration or Sezary cell count monitoring. Serial measurements of serum sIL-2Rα levels in adult patients with advanced lung cancer submitted to polychemotherapy were also shown to be very useful in disease monitoring. Individuals not responding to treatment exhibited persistent high levels of the receptors, while good responders did not (Brunetti et al. 1999). In the report of

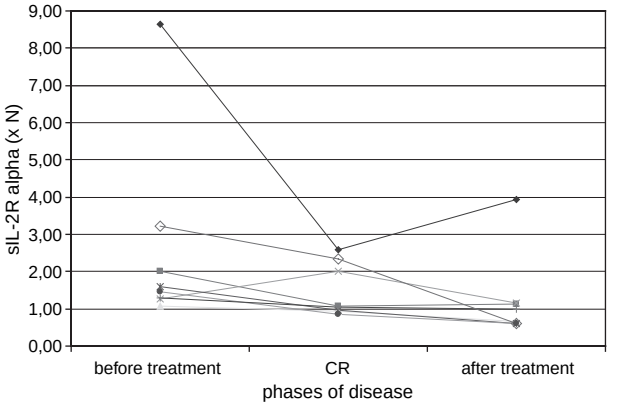

Figure 1. Individual curves of treatment monitoring in eight children with solid malignancies who underwent serial determinations of serum soluble IL-2Rα at all three phases of disease.

Fierro et al. (1992) a significant fall in serum soluble IL-2 receptor levels after therapy was seen in patients with advanced malignant melanoma responding to chemotherapy, confirming the usefulness of this parameter in monitoring disease evolution. Several other studies found no clinical significance of serial sIL-2Rα measurements during therapy in patients with solid malignant neoplasms. They included patients with ovarian cancer (Pavlidis et al. 1995) and nasopharyngeal carcinoma (Wu et al. 1998).

The only study concerning the significance of sIL-2Rα in treatment monitoring among children with neoplastic disorder is by Komp et al. (1989). Chemotherapy applied to nine patients with haemophagocytic histiocytic syndrome resulted in a dramatic reduction of pretreatment sIL-2Rα levels towards the normal range that was established for each particular age of the patients at the time of the examinations. The limitation of this report is the very small number of patients included in the study and the fact that not all the patients were examined at all stages of disease. There have been no reports published to date on the role of serum Tac antigen monitoring in children affected by malignant solid neoplasms.

As the elevation of sIL-2Rα in most solid tumours is thought to be an effect of the increased shedding from lymphocytes activated by tumour growth, it may be expected that many conditions during therapy are capable of stimulating the immune responsiveness of cancer patients. This may lead to the significant increase in serum sIL-2Rα levels. These conditions include radiotherapy (Ambrosetti et al. 1993), general anaesthesia (Brand et al. 2001, Schneemilch & Bank 2001), surgical procedures (Brivio et al. 1991), neutropenia-related infections (Soker et al. 2001) and haematopoietic growth factors (G-CSF) administration (Kobayashi et al. 1999, Stasi et al. 1994). To avoid the possible influence of these factors on serum levels of sIL-2Rα determined during anti-tumour treatment, we arranged precisely the points at which samples were collected in our patients. All sIL-2Rα measurements were performed at least 30 days after general anaesthesia and surgical procedures and at least 14 days after stopping the infection and/or G-CSF administration. The problem of age-related changes in sIL-2Rα levels has been discussed above.

Our observations on the clinical significance of sIL-2Rα in the group of 18 children suffering from WT and SA indicate that serial determinations of sIL-2Rα may be of importance in monitoring the response to anti-tumour therapy. This finding is of special value as these two histological types of paediatric malignant solid neoplasms lack any reliable, sensitive and specific biochemical tumour marker.

References

Ambrosetti A, Nadali G, Vinante F, Carlini S, Veneri D, Todeschini G, Morosato L, Sabata de D, Chilosi M, Maggi E, Parronchi P, Romagnani S, Semenzato G, Perona G, Pizzolo G. 1993. Serum levels of soluble interleukin-2 receptor in Hodgkin disease. Cancer 72:201–206.

Armitage RJ, Lai AP, Roberts PJ, Cawley JC. 1986. Certain myeloid cells possess receptors for interleukin-2. British Journal of Haematology 4:799–807.

Bodey B, Psenko V, Lipsey AL, Kaiser HE. 1996. Soluble interleukin-2 receptors in sera of children with primary malignant neoplasms. Anticancer Research 16:219–224.

Boyano MD, Garcia-Vazquez MD, Gardeazabal J, Garcia de Galdeano A, Smith-Zubiaga I, Canavate ML, Raton JA, Bilbao I, Diaz-Perez JL. 1997. Serum-soluble IL-2 receptor and IL-6 levels in patients with melanoma. Oncology 54:400–406.

Brand JM, Schmucker P, Breidthardt T, Kirchner H. 2001. Upregulation of IFN-gamma and soluble interleukin-2 receptor release and altered serum cortisol and prolactin concentration during general anesthesia. Journal of Interferon and Cytokine Research 21:793–796.

Brivio F, Lissoni P, Mancini D, Tisi E, Tancini G, Barni S, Nociti V. 1991. Effect of antitumor surgery on soluble interleukin-2 receptor serum levels. American Journal of Surgery 161:466–469.

Brunetti G, Bossi A, Baiardi P, Jedrychowska I, Pozzi U, Bacchella L, Bernardo G. 1999. Soluble interleukin 2 receptor (sIL2R) in monitoring advanced lung cancer during chemotherapy. Lung Cancer 23:1–9.

Chilosi M, Semenzato G, Getto G, Ambrosetti A, Fiore-Donati L, Perona G, Berton G, Lestani M, Scarpa A, Agostini C, Trentin L, Zambello R, Masciarelli M, Dazzi F, Vinante F, Caligaris-Cappio F, Pizzolo G. 1987. Soluble interleukin-2 receptors in the sera of patients with hairy cell leukemia: Relationship with the effect of recombinant α-interferon therapy on clinical parameters and natural killer in vitro activity. Blood 70:1530–1535.

Djeu JY, Liu JH, Wei S, Rui H, Pearson CA, Leonard WJ, Blanchard DK. 1993. Function associated with IL-2 receptor-β on human neutrophils. Journal of Immunology 150:960–970.

Espinoza-Delgado I, Ortaldo JR, Winkler-Pickett R, Sugamura K, Varesio L, Longo DL. 1990. Expression and role of p75 interleukin 2 receptor on human monocytes. Journal of Experimental Medicine 171:1821–1826.

Fierro MT, Lisa F, Novelli M, Bertero M, Bernengo MG. 1992. Soluble interleukin-2 receptor, CD4 and CD8 levels in melanoma: a longitudinal study. Dermatology 184:182–190.

Gutgsell NS, Malek TR. 1994. Formation of high affinity IL-2 receptors is dependent on a nonligand binding region of the α subunit. Journal of Immunology 153:3899–3907.

Honda M, Kitamura K, Takeshita T, Sugamura K, Tokunaga T. 1990. Identification of a soluble IL-2 receptor β-chain from human lymphoid cell line cells. Journal of Immunology 145:4131–4135.

Izzo F, Cremona F, Delrio P, Leonardi E, Castello G, Pignata S, Daniele B, Curley SA. 1999. Soluble interleukin-2 receptor levels in hepatocellular cancer: a more sensitive marker than alfa fetoprotein. Annals of Surgical Oncology 6:178–185.

Janik JE, Morris JC, Pittaluga S, McDonald K, Raffeld M, Jaffe ES, Grant N, Gutierrez M, Waldmann TA, Wilson WH. 2004. Elevated serum-soluble interleukin-2 receptor levels in patients with anaplastic large cell lymphoma. Blood 104:3355–3357.

Kallio JP, Tammela TL, Marttinen AT, Kellokumpu-Lehtinen PL. 2001. Soluble immunological parameters and early prognosis of renal cell cancer patients. Journal of Experimental and Clinical Cancer Research 20:523–528.

Kawashima O, Kamiyoshihara M, Sakata S, Endo K, Saito R, Morishita Y. 2000. The clinicopathological significance of preoperative serum-soluble interleukin-2 receptor concentrations in operable non-small-cell lung cancer patients. Annals of Surgical Oncology 7:239–245.

Kobayashi S, Imamura M, Hashino S, Noto S, Mori A, Tanaka J, Naohara T, Kasai M, Asaka M. 1999. Possible role of granulocyte colony-stimulating factor in increased serum soluble interleukin-2 receptor-α levels after allogenic bone marrow transplantation. Leukemia and Lymphoma 33:559–566.

Komp DM, Shapiro E, McNamara J. 1988. Soluble interleukin-2 receptor in childhood non-Hodgkin's lymphoma. Blood 71:1172–1174.

Komp DM, McNamara J, Buckley P. 1989. Elevated soluble interleukin-2 receptor in childhood hemophagocytic histiocytic syndromes. Blood 73:2128–2132.

Marcon L, Rubin LA, Kurman CC, Fritz ME, Longo DL, Uchiyama T, Edwards BK, Nelson DL. 1988. Elevated serum levels of soluble tac peptide in adult T-cell leukemia: correlation with clinical status during chemotherapy. Annals of Internal Medicine 109:274–279.

Moon Y, Kim Y, Kim M, Lim J, Kang CS, Kim WI, Shim SI, Chung NG, Park YH, Min WS, Han K. 2004. Plasma soluble interleukin-2 receptor (sIL-2R) levels in patients with acute leukemia. Annals of Clinical and Laboratory Science 34:410–415.

Morgan DA, Ruscetti FW, Gallo R. 1976. Selective *in vitro* growth of T-lymphocytes from normal human bone marrow. Science 193:1007–1009.

Murakami S, Sakata H, Tsuji Y, Okubo K, Hamada S, Hirayama R. 2002. Serum soluble interleukin-2 receptor as a predictor of lymph node metastasis in early gastric cancer. Digestive Surgery 19:9–15.

Murakami S. 2004. Soluble interleukin-2 receptor in cancer. Frontiers in Bioscience 9:3085–3094.

Nakase K, Tsuji K, Tamaki S, Tanigawa M, Ikeda T, Miyanishi E, Shiku H. 2005. Elevated levels of soluble interleukin-2 receptor in serum of patients with hematological or non-hematological malignancies. Cancer Detection and Prevention 29:256–259.

Naveau S, Balian A, Degos F, Daurat V, Chevret S, Gayno S, Bastie A, Riachi G, Bartolomei-Portal I, Barange K, Moussalli J, Bailly F, Chaumet-Riffaud P, Emilie D. 1999. Prognostic value of the soluble interleukin-2 receptor in chronic hepatitis C treated with interferon-alfa. Journal of Hepatology 31: 612–617.

Pavlidis NA, Bairaktari E, Kalef-Ezra J, Nicolaides C, Seferiadis C, Fountzilas G. 1995. Serum soluble interleukin-2 receptors in epithelial ovarian cancer patients. International Journal of Biological Markers 10:75–80.

Peteiro-Cartelle FJ, Alvarez-Jorge A. 1999. Dynamic profiles of interleukin-6 and the soluble form of CD25 in burned patients. Burns 25:487–491.

Pui C-H, Ip SH, Kung P, Dodge RK, Berard CW, Crist WM, Murphy SB. 1987. High serum interleukin-2 receptor levels are related to advanced disease and a poor outcome in childhood non-Hodgkin's lymphoma. Blood 70:624–628.

Pui C-H, Ip SH, Iflah S, Behm FG, Grose BH, Dodge RK, Crist WM, Furman WL, Murphy SB, Rivera GK. 1988. Serum interleukin 2 receptor levels in childhood acute lymphoblastic leukemia. Blood 71:1135–1137.

Pui C-H, Ip SH, Thompson E, Wilimas J, Brown M, Dodge RK, Hoyos de RA, Berard CW, Crist WM. 1989. High serum interleukin-2 receptor levels correlate with a poor prognosis in children with Hodgkin's disease. Leukemia 3:481–484.

Pui C-H, Hudson M, Luo X, Wilimas J, Evans W, Crist WM. 1993. Serum interleukin-2 receptor levels in Hodgkin disease and other solid tumors of childhood. Leukemia 7:1242–1244.

Rubin LA, Kurman CC, Fritz ME, Biddison WE, Boutin B, Yarchoan R, Nelson DL. 1985. Soluble interleukin 2 receptors are released from activated human lymphoid cells in vitro. Journal of Immunology 135:3172–3177.

Rubin LA, Jay G, Nelson DL. 1986. The released interleukin 2 receptor binds interleukin 2 efficiently. Journal of Immunology 137:3841–3844.

Rubin LA, Nelson DL. 1990. The soluble interleukin-2 receptor: biology, function, and clinical application. Annals of Internal Medicine 113:619–627.

Rutkowski P, Kaminska J, Kowalska M, Ruka W, Steffen J. 2002. Cytokine serum levels in soft tissue sarcoma patients: correlations with clinico-pathological features and prognosis. International Journal of Cancer 100:463–471.

Schneemilch CE, Bank U. 2001. Release of pro- and anti-inflammatory cytokines during different anesthesia procedures. Anaesthesiologie und Reanimation 26:4–10.

Sakata H, Murakami S, Hirayama R.. 2002. Serum soluble interleukin-2 receptor (IL-2R) and immunohistochemical staining of IL-2R/Tac antigen in colorectal cancer. International Journal of Clinical Oncology 7:312–317.

Sedlaczek P, Frydecka I, Gabrys M, Van Dalen A, Einarsson R, Harlozinska A. 2002. Comparative analysis of CA125, tissue polypeptide specific antigen, and soluble interleukin-2 receptor alpha levels in sera, cyst, and ascitic fluids from patients with ovarian carcinoma. Cancer 95:1886–1893.

Sharma S, Saha K, Shinghal RN, Malik GB.. 1991. Serum soluble interleukin-2 (IL-2) receptor levels in women with breast carcinoma and its correlation with IL-2 receptor expression on blood lymphocytes and lymphocytic infiltration within the tumour. Cancer Immunology, Immunotherapy 33:198–202.

Shi H-Z, Sun J-J, Pan H-L, Lu J-Q, Zhang J-L, Jiang J-D. 1999. Alterations of T-lymphocyte subsets, soluble IL-2 receptor, and IgE in peripheral blood of children with acute asthma attacks. Journal of Allergy and Clinical Immunology 103:388–394.

Soker M, Colpan L, Ece A, Devecioglu C, Haspolat K. 2001. Serum levels of IL-1 beta, sIL-2R, IL-6, IL-8, and TNF-alpha in febrile children with cancer and neutropenia. Medical Oncology 18:51–57.

Sondel PM. 1997. Tumor immunology and pediatric cancer. In: Pizzo PA, Poplack DG, editors. Principles and Practice of Pediatric Oncology. Philadelphia: Lippincott-Raven Publishers. p. 103–128.

Stasi R, Zinzani PL, Galieni P, Lauta VM, Damasio E, Dispensa E, Dammacco F, Tura S, Papa G. 1994. Detection of soluble interleukin-2 receptor and interleukin-10 in the serum of patients with aggressive non-Hodgkin's lymphoma. Cancer 74:1792–1800.

Sugamura K, Takeshita T, Asao H, Kumaki S, Ohbo K, Ohtani K, Nakamura M. 1990. IL-2-induced signal transduction: involvement of tyrosine kinase and IL-2 receptor γ chain. Lymphokine Research 9: 539–547.

Tartour E, Mosseri V, Jouffroy T, Deneux L, Jaulerry C, Brunin F, Fridman WH, Rodriguez J. 2001. Serum soluble interleukin-2 receptor concentrations as an independent prognostic marker in head and neck cancer. Lancet 357:1263–1264.

Trentin L, Zambello R, Bulian P, Cerutti A, Milani A, Pirone E, Nitti D, Agostini C, Semenzato G. 1994. Functional role of IL-2 receptors on tumour-infiltrating lymphocytes. British Journal of Cancer 69: 1046–1051.

Viviani S, Camerini E, Bonfante V, Santoro A, Balzarotti M, Fornier M, Devizzi L, Verderio P, Valagussa P, Bonadonna G. 1998. Soluble interleukin-2 receptors (sIL-2R) in Hodgkin's disease: outcome and clinical implications. British Journal of Cancer 77:992–997.

Vonderheid EC, Zhang Q, Lessin SR, Polansky M, Abrams JT, Bigler RD, Wasik MA. 1998. Use of serum soluble interleukin-2 receptor levels to monitor the progression of cutaneous T-cell lymphoma. Journal of the American Academy of Dermatology 38:207–220.

Wakao D, Murohashi I, Tominaga K, Yoshida K, Kishimoto K, Yagasaki F, Itoh Y, Itoh K, Sakata T, Kawai N, Kayano H, Suzuki T, Matsuda A, Hirashima K, Bessho M. 2002. Serum thymidine kinase and soluble interleukin-2 receptor predict recurrence of malignant lymphoma. Annals of Hematology 81:140–146.

Waldmann TA, Pastan IH, Gansow OA, Junghans RP. 1992. The multichain interleukin-2 receptor: a target for immunotherapy. Annals of Internal Medicine 116:148–160.

Wang LS, Chow KC, Li WY, Liu CC, Wu YC, Huang MH. 2000. Clinical significance of serum soluble interleukin 2 receptor-alpha in esophageal squamous cell carcinoma. Clinical Cancer Research 6: 1445–1451.

Wu LJ, Chen KY, Chi KH, Chen SY, Liang MJ, Shiau CY, Wang LW, Liu YM, Chow KC, Yen SH. 1998. The significance of soluble interleukin-2 receptor in monitoring disease relapse in patients with nasopharyngeal cancer. Japanese Journal of Clinical Oncology 28:729–732.