Soluble Interleukin-2 Receptor: A Useful Prognostic Factor for Patients With Hemophagocytic Lymphohistiocytosis

To the Editor:

Elevation of serum concentrations of soluble interleukin-2 receptor (sIL-2R) has been shown in various hematolymphoid malignancies. Since its first documentation by Komp et al. in 1989, sIL-2R has also been measured and tested for clinical usefulness as a prognostic indicator for patients with hemophagocytic lymphohistiocytosis (HLH). However, these studies evaluated a small number of patients.

In this study, we analyzed data on 74 HLH cases, including 71 children and 3 adults, that were collected over the past 10 years (Table 1). Diagnosis of all cases was compatible with the criteria of Henter et al. In the majority of cases, high serum concentration of ferritin (>1,000 ng/mL) and/or high lactate dehydrogenase (>1,000 IU/L) was shown. sIL-2R was determined by an enzyme immunoassay kit from T Cell Science (Cambridge, MA; normal values, <1,090 U/mL for children and <860 U/mL for adults) and interferon (IFN)-γ was assayed by Celltech Diagnostics (Birksire, UK) SUCROSEP IFN-γ immunoradiometric assay or human γ-IFN RIA kit (Centecor Inc, Malvern, PA; values adjusted for Celltech, with normal values <1.0 U/mL).

During the active phase of the disease, the serum concentrations of sIL-2R ranged from 465 to 93,500 U/mL in these cases. Seventy-one of the 74 cases displayed elevated values. Forty cases showed sIL-2R levels greater than 10,000 U/mL (designated group A), whereas the remaining 34 cases had levels of less than 10,000 U/mL (group B). In a comparison of data for these two groups, median age was nearly the same (2 years) and female predominance in group A was not significant. Simultaneous hyper-IFN-γ-nemia (IFN-γ >4.5 U/mL) and the number of patients requiring treatment with chemotherapy such as etoposide and prednisone was associated significantly with group A. Group B showed a significantly better (Log rank, \( P = .0001 \)) 5-year survival over group A, as calculated using the Kaplan-Meier analysis (Fig 1); 78.1% (95% CI, 94.1% to 62.1%) for group B versus 36.1% (95% CI, 51.3% to 20.9%) for group A. Although it may seem contradictory for patients in group A who received more chemotherapy than those in group B to show a worse prognosis, 9 of the 36 chemotherapy-treated cases in group A did not receive complete treatment due to severe clinical conditions and died before the effect of chemotherapy could be evaluated. When these 9 cases are excluded from group A, the number of cases treated with chemotherapy were comparable for two groups (27/40 for group A v 15/34 for group B, \( P = .07 \), Table 1), probably suggesting no impact of chemotherapy on the poor prognosis in group A. The high association of elevated serum sIL-2R with occurrence of hyper-IFN-γ-nemia in group A indicates that activated T cells and/or natural killer cells are involved in the pathogenesis of HLH.

Table 1. Comparison of Clinical Data on Two Groups of HLH Cases Based on sIL-2R Concentrations

<table>
<thead>
<tr>
<th>Group A (sIL-2R &gt;10,000)</th>
<th>Group B (sIL-2R &lt;10,000)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n)</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>Age; median (range)</td>
<td>2 yr, 8 mo</td>
<td>2 yr (1 mo-15 yr)</td>
</tr>
<tr>
<td></td>
<td>(1 mo-62 yr)</td>
<td>15 yr</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>13/27</td>
<td>18/16</td>
</tr>
<tr>
<td>Hyper-IFN-γ-nemia*</td>
<td>33/39</td>
<td>11/34</td>
</tr>
<tr>
<td>Chemotherapy used</td>
<td>38/40</td>
<td>15/34</td>
</tr>
<tr>
<td>5-yr survival</td>
<td>36.1%</td>
<td>78.1%</td>
</tr>
</tbody>
</table>

* No data are available in 1 case.
† When 9 cases were excluded from group A because of incomplete chemotherapy, the difference between two groups is not significant.

Fig 1. Survival from onset of disease comparing patients with sIL-2R levels greater than 10,000 IU/mL (A) and less than 10,000 IU/mL (B) sIL-2R.
killer (NK) cells play a major role as underlying immunologic disorders and that serum IFN-γ levels are also a good prognostic parameter for HLH cases as determined by Kaplan-Meier analysis for hyper-IFN-γ-nemic cases (n = 44) versus no-hyper-IFN-γ-nemic cases (n = 39; data for 1 case not available), which showed a significantly poor 5-year survival for hyper-IFN-γ-nemic cases (45.0% vs 70.6%, P = 0.023), confirming the results of our previous report. It was also underscored in this study that 54% of the HLH cases showed a greater than 10,000 U/mL level of sIL-2R, indicating that HLH is characterized by a remarkably elevated level of serum sIL-2R, compared with previously reported data for various hematolymphoid malignancies.

The prognosis of patients with HLH is very poor. In fact, 30 (40.5%) of these 74 cases have died to date. Innovative therapeutic devices are required to improve patient outcome for these hypercytokinemia-related disorders. Our data clearly suggest that measurement of serum sIL-2R in cases of HLH is a useful means for prompt prediction of prognosis, so that the optimal treatment for these patients can be selected with HLH.

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REFERENCES


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