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.\(^1\) Since its first documentation by Komp et al\(^2\) in 1989, sIL-2R has also been measured and tested for clinical usefulness as a prognostic indicator for patients with hemophagocytic lymphohistiocytosis (HLH).\(^3\) 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.\(^4\) 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 (Birkshire, UK) SUCROSEP IFN-γ immunoradiometric assay or human γ-IFN RIA kit (Cenctor 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.

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

<table>
<thead>
<tr>
<th></th>
<th>Group A (sIL-2R ≥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>
<td></td>
</tr>
<tr>
<td>Age; median (range)</td>
<td>2 yr, 8 mo</td>
<td>2 yr (1 mo-15 yr)</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>13/27</td>
<td>18/16</td>
<td></td>
</tr>
<tr>
<td>Hyper-IFN-γ–nemia*</td>
<td>33/39</td>
<td>11/34</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Chemotherapy used</td>
<td>361/40</td>
<td>15/34</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>5-yr survival</td>
<td>36.1%</td>
<td>78.1%</td>
<td>.0001</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 ≥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 (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% v 70.6%, P = .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.

REFERENCES


Soluble interleukin-2 receptor: a useful prognostic factor for patients with hemophagocytic lymphohistiocytosis [letter]

S Imashuku, S Hibi, M Sako, Y Ishida, H Mugishima, J Chen and Y Tsunematsu

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