Interleukin-6 and Soluble Interleukin-6 Receptor Levels as Markers of Disease Extent and Prognosis in Neuroblastoma

Rachel A. Egler, Susan M. Burlingame, Jed G. Nuchtern, and Heidi V. Russell

Abstract

Purpose: To explore the relationships between interleukin-6 (IL-6) and soluble IL-6 receptor (sIL-6R) levels and disease extent and clinical outcome in childhood neuroblastoma.

Experimental Design: Pretreatment peripheral blood (PB; n = 53) and bone marrow (n = 18) samples from patients with neuroblastoma were assayed by ELISA for IL-6 and sIL-6R. PB values were compared with healthy pediatric controls (n = 28).

Results: PB IL-6 levels were significantly elevated in patients with high-risk disease compared with those with low and intermediate risk disease (23.9 versus 4.3 pg/mL; P < 0.001) and the normal control group (23.9 versus 3.3 pg/mL; P < 0.001). Similarly, bone marrow IL-6 levels were higher in high-risk patients when compared with low- and intermediate-risk patients (15 versus 0 pg/mL; P < 0.02). Other factors correlated with higher IL-6 levels were age of >18 months, bony metastases, and unfavorable histology. sIL-6R levels were not significantly correlated with disease stage. Patients with detectable PB IL-6 at diagnosis had significantly lower event-free survival rates (P = 0.008). sIL-6R levels >2.5 pg/mL were also associated with a significantly worse event-free survival (P = 0.016).

Conclusion: Elevated PB IL-6 levels correlated with features of high-risk neuroblastoma and poor prognosis in this population. Decreased PB sIL-6R levels correlated with the presence of metastatic disease. Further study of these markers in children with neuroblastoma seems warranted.

Neuroblastoma, the most common extracranial solid tumor of childhood, accounts for 8% to 10% of all childhood cancers (1, 2). The complex biological and clinical features of neuroblastoma have allowed for the development of a risk-based model for staging and treatment of these patients (3, 4). For example, low-risk tumors are often well-circumscribed lesions, which occur in younger patients, can be treated with surgery alone, and are curable in over 90% of patients (2, 5). In contrast, patients with high-risk disease are typically older patients who have histologically aggressive tumors that have often spread to the bone and bone marrow (BM) at the time of diagnosis. Despite intensive chemotherapy, radiation, and surgery, patients with these tumors have significantly worse survival rates in the range of 30% to 40% (6, 7). Low-risk and high-risk tumor types each make up ~40% to 45% of neuroblastoma diagnoses. The remaining 10% to 5% of tumors are classified as intermediate risk. As the name implies, they have a mix of both good and poor prognostic factors. Their survival rates are a little lower than those of low risk tumors at 85% to 95% overall survival (4, 8).

Interleukin 6 (IL-6) is a pleiotropic cytokine with many ascribed effects including stimulation of acute phase reactants, immunoregulation, angiogenesis, and osteoclast activation (9–12). It originates from a multitude of cell types, including mononuclear phagocytes, vascular endothelial cells, fibroblasts, hepatocytes, B-cell lymphomas, and the neoplastic plasma cells of multiple myeloma. It seems to serve as a stimulatory factor in multiple myeloma; it is produced by both the malignant cells and BM stromal cells (11). In neuroblastoma, some literature indicates production of IL-6 by neuroblastoma cell lines (13, 14); however, a more recent article asserts IL-6 is produced by mesenchymal stem cells in the marrow microenvironment of neuroblastoma (10).

IL-6 has a dedicated receptor that can be found either on the cell membrane or in a solubilized form (sIL-6R; refs. 9, 12). The receptor will bind IL-6 in the circulation as well as at the cellular membrane. The receptor complex bends to the GP-130 transmembrane receptor (9, 15). This, then, activates multiple pathways, the most described of which is the Stat3 pathway (15, 16). Stat3 has been shown to play a role in delaying the initiation of an inflammatory response to cancer as it develops (15, 17). Along with IL-6, multiple myeloma cells also produce sIL-6R. sIL-6R antibodies have been studied as targeted therapy in multiple myeloma (18, 19).

Both circulating IL-6 and sIL-6R can be detected in the peripheral blood (PB). Increased levels of IL-6 at diagnosis
have been associated with advanced disease and poor outcome in multiple neoplasms including prostate cancer (20), non–Hodgkin’s lymphoma (21, 22), head and neck squamous cell carcinoma (23), breast cancer (24), melanoma (25, 26), and multiple myeloma (11). The prognostic value of sIL-6R levels is less well-established. It has been investigated as part of biochemical staging in prostate cancer and as a prognostic factor in multiple myeloma (27, 28).

Taking together the evidence of circulating IL-6 and sIL-6R levels as markers of poor prognosis in other cancers, as well as the implication of IL-6 activity in the microenvironment of neuroblastoma, we hypothesized that both IL-6 and sIL-6R levels would be elevated in children with neuroblastoma compared with normal controls. Additionally, we hypothesized that the degree of IL-6 and sIL-6R elevation would be related to the aggressiveness of the neuroblastoma. We therefore investigated the levels of IL-6 and sIL-6R in patients with newly diagnosed neuroblastoma and a healthy pediatric population.

Translational Relevance

The following article describes levels of interleukin 6 (IL-6) and soluble IL-6 receptor (sIL-6R) in the peripheral blood and bone marrow of patients with neuroblastoma at diagnosis. The article finds that IL-6 and, to a lesser extent, sIL-6R, can differentiate patients with poor risk factors, e.g., high-risk disease and/or metastatic disease, from other neuroblastoma patients. The clinical relevance of these findings are 2-fold. First, IL-6 and sIL-6R may have roles as peripheral blood markers of active, aggressive disease neuroblastoma. Second, IL-6 and sIL-6R may have use in neuroblastoma as a new therapeutic pathway. If, as the literature suggests, IL-6 is mediating the aggression and growth of neuroblastoma, elevated circulating levels of IL-6 and its receptor may identify patients for whom the IL-6 complex is a therapeutic target. Additionally, this article provides normal pediatric values for peripheral blood IL-6 and sIL-6R levels, which can be used for reference for future studies.

Materials and Methods

Sample collection. All the work described within this article was done with the approval of the Baylor College of Medicine Institutional Review Board. Texas Children’s Cancer Center has banked PB and BM samples from patients with neuroblastoma and ganglioneuroblastoma. For the purpose of this study, we retrospectively selected all samples collected between August 1995 and December 2005 for which the following clinical information was available: age at diagnosis, stage and sites of disease at diagnosis, relapse status, and time to last follow-up. In addition, we collected data regarding risk category (as defined by the Children’s Oncology Group risk stratification system; ref. 2) on all patients as well as described prognostic features as available. These features include tumor histology (Shimada favorable or unfavorable staging system; refs. 3, 4) and MYCN status (presence or absence of 10 or more copies of gene amplification in the tumor; refs. 3, 29). Collection of all samples used occurred at the time of diagnosis, before either the start of systemic chemotherapy or complete resection of the tumor. All PB samples were obtained as whole blood in heparin and separated into either plasma or serum. These were then aliquotted and stored at -80°C. BM aspiration samples were processed in a similar fashion.

The normal pediatric controls were collected in the following manner. Upon permission from the parent or guardian, whole blood was obtained from otherwise well children undergoing elective surgery such as hernia repair or circumcision. They had no identified infectious process at the time of surgery. The blood was processed in the same manner as described above.

IL-6 levels. IL-6 levels were determined using a human IL-6 BD OptEIA ELISA (BD Biosciences). This assay has a range of 4.7 to 300 pg/mL. One hundred microliters of each sample was prepared and tested as per the manufacturer’s instructions. Each sample was tested in duplicate, with the mean used for the final sample value. Mean values of <4.7 pg/dL were recorded as 0. Any sample with a value of >300 pg/mL was diluted and retested with appropriate adjustment of the final value.

sIL-6R levels. sIL-6R levels were determined using a Quantikine human IL-6 sR ELISA (R&D Systems, Inc.). The assay has a range of 31.2 to 1,000 pg/mL. Ten microliters of each sample was diluted by 100-fold and tested as per the manufacturer’s instructions. All samples were tested in duplicate, and the mean was used for the final sample value.

Statistical considerations. Means of IL-6 and sIL-6R levels were compared based on risk level, age, disease state, histology, MYCN amplification, and presence of metastatic disease in specific sites. Significance of difference in means was obtained using a nonparametric Mann-Whitney comparison. Overall sample sizes were chosen to reach a sample size of >17 in each group whenever possible. This size allowed for detection of at least one SD of difference with a power of 0.8 and an α of 0.05. Event-free survival (EFS) curves were generated by Kaplan Meiers analysis curves and compared via a log-rank test. All statistics were run using SPSS version 15 software. Any sample for which the sorting information was not known was left out of the analysis.

Results

Patient characteristics. Fifty-three PB and 18 BM samples collected at the time of diagnosis from patients with neuroblastoma were identified for inclusion in the study. This sample set represented 54 patients in total, with both blood and BM coming from 17 patients, blood only coming from 36 patients and BM only coming from 1 patient. In addition, we used 28 pediatric normal control plasma samples. The demographics of the patients and normal controls can be found in Table 1.

The median age of patients contributing samples for PB and/or BM was 21 and 23 mo, respectively. This is above the reported historical median age of patients with neuroblastoma of 18.7 mo (2). Although the median age of normal controls is higher than for patients (54 versus 21 mo), the range of ages shows a distribution that overlaps with the patient samples.

The range of characteristics such as stage, sites of disease, and biological prognostic factors were well-distributed among the PB samples. High-risk patients were more heavily represented in the BM samples (P = 0.021). MYCN amplification status and histology characteristics were not available for some samples as noted in Table 1.

Median follow-up time for patients contributing PB samples was 29 mo (range, 1-128 mo). Of these patients, 33% had disease relapse and nearly 20% died of their disease. Median follow-up time for patients contributing BM samples was 10 mo (range, 3-18 mo); of these, 3 patients (17%) had relapsed and 1 patient (6%) had died.

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IL-6 levels and disease status. Normal control PB samples had levels of IL-6 undetectable by our ELISA system in 26 of the 28 children. The remaining 2 had values of 10.3 and 82.3 pg/mL. PB levels of IL-6 from patients ranged from undetectable to 91.8 pg/mL. As shown in Fig. 1, there is a statistically significant difference in the levels of PB IL-6 in patients with high-risk disease when compared with those with low- and intermediate-risk disease (23.9 versus 4.3 pg/mL; \( P < 0.001 \)) and to the control group (23.9 versus 3.3 pg/mL; \( P < 0.001 \)).

Higher IL-6 levels were also present in the BM samples of children with high-risk disease when compared with patients with low- and intermediate-risk disease (15 pg/mL versus undetectable; \( P < 0.02 \); see Fig. 1B).

Table 2 shows comparisons of PB and BM IL-6 values in patients when categorized by age, presence or absence of metastatic disease (bone and/or BM), MYCN amplification, and histology. This table illustrates several trends. First, although IL-6 levels in PB tend to be higher in patients with low- and intermediate-risk disease (15 pg/mL versus undetectable; \( P < 0.02 \); see Fig. 1B).

Table 2 shows comparisons of PB and BM sIL-6R values in patients when stratified by age, presence or absence of metastatic disease (bone and/or BM), MYCN amplification, and histology. This table illustrates that metastatic disease at diagnosis was associated with a significantly lower PB sIL-6R level (2.8 versus 3.9 \( \times 10^6 \) pg/mL; \( P = 0.04 \)). However, this trend was not apparent in the BM (2.4 versus 3.9 \( \times 10^6 \) pg/mL; \( P = 0.05 \); Fig. 1C and D). As with the IL-6 levels, the PB normal controls were similar to the low- and intermediate-risk disease group with an average level of 3.4 \( \times 10^6 \) pg/mL.

Table 2 shows comparisons of PB and BM sIL-6R values in patients when stratified by age, presence or absence of metastatic disease (bone and/or BM), MYCN amplification, and histology. This table illustrates that metastatic disease at diagnosis was associated with a significantly lower PB sIL-6R level (2.8 versus 3.9 \( \times 10^6 \) pg/mL; \( P = 0.04 \)). However, this trend was not apparent in the BM (2.4 versus 3.9 \( \times 10^6 \) pg/mL; \( P = 0.05 \); Fig. 1C and D). As with the IL-6 levels, the PB normal controls were similar to the low- and intermediate-risk disease group with an average level of 3.4 \( \times 10^6 \) pg/mL.
levels were consistently lower in the patients with poor prognostic features.

Levels and survival. We assessed IL-6 and sIL-6R PB levels in patients with neuroblastoma at diagnosis and their relationship to EFS. Patients with a PB IL-6 level of >0 pg/mL at the time of diagnosis had a significantly lower EFS rate (log-rank \( P < 0.008 \); Fig. 2A). When analyzing high risk patients only, the difference in EFS is lost (Fig. 2B). For sIL-6R levels, there is a significant difference in EFS between the patients with sIL-6R levels lower than \( 2.5 \times 10^4 \) pg/mL compared with those higher (\( P = 0.016 \); Fig. 2C). The level \( 2.5 \times 10^4 \) pg/mL represents the cutoff for the lowest third of sIL-6R values obtained. Again, this significance is lost when only the high-risk patients are included (Fig. 2D).

**Discussion**

Our data show that patients with neuroblastoma who have elevated PB levels of IL-6 at diagnosis tend to have high-risk disease and generally poor outcomes. Also, IL-6 BM levels were significantly increased in high-risk patients. In addition, sIL-6R levels followed an inverse relationship with disease such that lower levels were present in the PB of patients with high-risk disease, although this trend was not statistically significant. Peripheral blood sIL-6R levels were significantly lower in patients presenting with metastatic disease compared with those with only local disease. Finally, we presented PB IL-6 and sIL-6R levels for healthy pediatric patients.

Multiple studies have shown a role for elevated IL-6 levels at diagnosis as a marker of poor prognosis in various cancers including multiple myeloma (11), malignant melanoma (25, 26), non–Hodgkin’s lymphoma (21, 22), prostate cancer (20), squamous cell carcinoma of the head and neck (23), and various sarcomas (30, 31). In this article, we have shown that patients with neuroblastoma who have elevated levels of IL-6 at diagnosis also have features of high-risk disease, including unfavorable histology, metastatic disease in general, and specifically, in the presence of BM disease. Additionally, patients with elevated IL-6 have decreased EFS when compared with those without. Patients with MYCN amplification do not have significantly different IL-6 levels at presentation.

![Fig. 1. Levels of IL-6 and sIL-6R in the blood and BM. A, levels of IL-6 in the PB of patients with low- and intermediate-risk neuroblastoma, high-risk neuroblastoma, and healthy pediatric controls. *, extreme outliers. B, levels of IL-6 in the BM of patients with low- and intermediate-risk neuroblastoma compared with high risk. C, levels of sIL-6R in the PB of patients with low and intermediate-risk neuroblastoma, high-risk neuroblastoma, and healthy pediatric controls. *, outlier values. D, levels of sIL-6R in the BM of patients with low- and intermediate-risk neuroblastoma compared with high risk.](http://www.aacrjournals.org)
proposing that IL-6 stimulates proliferation and survival of activation. This same group has added to the picture by mal cells to secrete IL-6, which in turn caused osteoclast come from the bony microenvironment. The presence of work, it was proposed that the IL-6 present in the BM may themselves are not the source of the IL-6 (10). In the same failed to show IL-6 mRNA, suggesting that the tumor cells mentioned in the introduction, some cell line work has available for study. For this reason, we are unable to draw conclusions from this work as to whether the BM microenviroment as evidenced by the persistent presence of tumor. The consistency of IL-6 level elevations in the blood than those without, suggesting elevated levels are independent of this known risk factor. It is not, however, independent of the current overall risk stratification system as patients classified as high risk have significantly higher IL-6 levels at diagnosis.

When we investigated BM as a potential microenvironment source for the IL-6, the marrow levels were again significantly increased when samples were stratified by the patient’s risk category. BM IL-6 levels in patients with metastatic disease and specifically those with cortical bone lesions approached significance but did not achieve it. One potential cause for the lack of significance may be the number of BM samples available for study. For this reason, we are unable to draw conclusions from this work as to whether the BM microenvironment is a source of IL-6. It is unclear where the source of the IL-6 lies in neuroblastoma, although it is likely that there is more than one source at play. Given its pleiotropic nature, it is possible that the PB IL-6 levels are indicative of a systemic response to the tumor. The consistency of IL-6 level elevations in the blood more than the BM would support this. Still, the IL-6 may be coming from the tumor or the tumor microenvironment. As mentioned in the introduction, some cell line work has supported constitutive production of IL-6 by neuroblastoma cell lines (14, 32). More recently, although, it has been published that PCR analysis of five neuroblastoma cell lines failed to show IL-6 mRNA, suggesting that the tumor cells themselves are not the source of the IL-6 (10). In the same work, it was proposed that the IL-6 present in the BM may come from the bony microenvironment. The presence of neuroblastoma cells was shown to induce the BM mesenchymal cells to secrete IL-6, which in turn caused osteoclast activation. This same group has added to the picture by proposing that IL-6 stimulates proliferation and survival of neuroblastoma cells in the BM microenvironment (33). This would suggest that the elevated levels seen in the presence of metastatic disease are part of a neuroblastoma-stimulated pro-proliferation loop similar to the one seen in multiple myeloma. In comparison to IL-6 levels, sIL-6R levels followed an inverse relationship with disease such that lower levels were present in the PB of patients with metastatic disease and with BM disease. This finding was in contrast to previously published work in prostate cancer, which showed an increase in sIL-6R levels was a poor prognostic factor (27). We were not able to correlate IL-6 levels with sIL-6R levels either directly or inversely in individual patients (data not shown). Although sIL-6R levels varied in the BM samples, we found no correlation with disease state. As with IL-6, two potential roles for sIL-6R emerge from these data. The first is as a systemic consumption response to aggressive disease as evidenced by the decreased circulating levels. In this model, the sIL-6R levels are decreased in the presence of metastatic disease. The second potential role is as part of the BM microenvironment as evidenced by the persistent presence of sIL-6R in the BM. These observations add to the argument that the IL-6 pathway functions in multiple ways in neuroblastoma.

We postulate that the significance of elevated circulating levels of IL-6 and decreased circulating levels of sIL-6R in neuroblastoma is 2-fold. First, IL-6 and its receptor may have roles as PB markers of active, aggressive disease in neuroblstaoma. Although IL-6 and sIL-6R levels do not stratify patients at diagnosis independent of the already established risk categorization, they may prove beneficial as indicators of active disease, which could be used to monitor patients for relapse. Many techniques have been described as markers for residual or returning disease in patients with neuroblastoma.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IL-6 (pg/mL)</th>
<th>sIL-6R (×10⁴ pg/mL)</th>
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<tbody>
<tr>
<td></td>
<td>PB</td>
<td>BM</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Mean ± SE</td>
</tr>
<tr>
<td><strong>Age (mo)</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt;18 mo</td>
<td>22</td>
<td>4.9 ± 2.3</td>
</tr>
<tr>
<td>≥18 mo</td>
<td>31</td>
<td>21.5 ± 4.8</td>
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<tr>
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</tr>
<tr>
<td>High</td>
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<td>23.9 ± 4.9</td>
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</tr>
<tr>
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</tr>
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<tr>
<td>Yes</td>
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<td>23.5 ± 5.9</td>
</tr>
<tr>
<td><strong>MYCN amplification</strong></td>
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<td></td>
</tr>
<tr>
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<td>13.5 ± 3.5</td>
</tr>
<tr>
<td>Amplified</td>
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<td>12.6 ± 4.3</td>
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<tr>
<td><strong>Histology</strong></td>
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<tr>
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<td>9</td>
<td>6 ± 4.4</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>12</td>
<td>16.4 ± 8</td>
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</table>
including immunocytology, reverse transcription-PCR, and flow cytometry (34, 35). These techniques, however, are dependent on the circulation of neuroblastoma cells for successful detection. As a circulating cytokine, which is a reaction to tumor growth, IL-6 and its receptor may represent useful alternatives to these techniques. As we have shown, they are readily detectable in the PB through a commercially available assay. This would follow the model of a marker such as ferritin, previously described as a prognostic marker in neuroblastoma (36, 37). The significant contrast between PB levels in the presence of high-risk disease compared with those in patients with low-risk disease or healthy pediatric controls along with the ease of the assay recommend further investigation into the utility of IL-6 and sIL-6R levels to monitor for tumor recurrence. To address this, a longitudinal study measuring IL-6 levels in a group of patients at diagnosis and then throughout treatment, remission, and relapse is indicated.

The second potential significance of IL-6 in neuroblastoma is as a new therapeutic pathway. If, as the literature suggests, IL-6 is mediating the aggression and growth of neuroblastoma, elevated circulating levels of IL-6 and its receptor may identify patients for whom the IL-6 complex is a therapeutic target. Anti–IL-6 and anti–IL-6 receptor agents have been studied in both preclinical and clinical trials with moderate success in multiple myeloma, where IL-6 is a stimulator of growth in a positive feedback loop fashion (18, 19, 38, 39). Additionally, tocilizumab, a humanized anti–IL-6 receptor antibody, has been trialed successfully in both adults and children with rheumatologic conditions, where IL-6 is known to play a role (40, 41). One potential downside to the use of IL-6 antagonists is brought up by the work of Hatziet al. (14), which suggested that IL-6 actually inhibits neuroblastoma angiogenesis and therefore acts to limit tumor size. Because of this potentially protective effect of IL-6, anti–IL-6 and anti–IL-6R agents will need to be investigated in closely in preclinical models before human use.

In addition to its discussion of IL-6 and sIL-6R in neuroblastoma patients, this article also presents normal pediatric PB IL-6 and sIL-6R levels. Although adult baseline

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**Fig. 2.** EFS in correlation with IL-6 and sIL-6R levels. All patients were included in this analysis. Patients were censored at the time of their last follow-up visit. **A.** EFS of all patients with neuroblastoma based on the presence or absence of IL-6 in the PB at diagnosis. **B.** EFS of patients with high-risk neuroblastoma only based on the presence or absence of IL-6 in the PB at diagnosis. **C.** EFS of all patients with neuroblastoma based on the level of sIL-6R present in the PB at diagnosis. **D.** EFS of patients with high-risk neuroblastoma only based on the level of sIL-6R present in the PB at diagnosis.
values were recently published (42), this is to our knowledge, the first time pediatric normal values have seemed in the literature. The range and mean values were similar to those seen in adult study.

To conclude, PB levels of IL-6 and sIL-6R may have a role as active disease markers in high-risk neuroblastoma. Further study of their roles in a larger cohort of patients with neuroblastoma is warranted.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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