Multilineage Immune-Mediated Cytopenias in Childhood: A Report of Five Patients

Cengiz CANPOLAT*, Steven CULBERT**, Hallie ZIETZ**, Keith HOOTS**

* Department of Pediatric Hematology Oncology, Marmara University Hospital, Istanbul, TURKEY
** Department of Clinical Pediatrics, University of Texas, M.D. Anderson Cancer Center, Texas, USA

ABSTRACT

This study was performed to determine whether there is any distinction to be made between single and multiple-lineage cytopenias particularly with regard to natural history and prognosis. From December 1989 to May 1994, five of 50 children (median age 7 years) with chronic immune cytopenias were diagnosed with multi-lineage immune-mediated cytopenias. Two patients presented with immune thrombocytopenia (ITP) and later developed autoimmune hemolytic anemia (AIHA); one had ITP and immune neutropenia who subsequently became Coombs’ positive but never developed AIHA. One child presented with ITP and immune neutropenia and later developed AIHA. The fifth child presented simultaneously with thrombocytopenia and neutropenia with positive antineutrophil antibody but without antplatelet antibody and Coombs’ positivity. Four patients were given primary therapy with IVIG and one with prednisone. One patient responded to prednisone but relapsed subsequently. Further treatment with IVIG produced initial normalization of his counts with occasional fluctuation of the absolute neutrophil count. Two responded to IVIG and are in complete remission (CR). Of the two nonresponders to IVIG, one responded subsequently to prednisone and is in CR. The other one, after being refractory to multimodality treatment, was diagnosed with a lupus erythematosis variant and is currently on alternate day prednisone. Moderate thrombocytopenia and absolute neutropenia still persist. Multi-lineage immune-mediated cytopenias may represent a pathogenic phenomenon that is distinct from autoimmune single-lineage disease. Clinical response to treatment may correlate with these differences that may be genetic in origin. Clinical course and response to therapy are less predictable when autoimmune disease is present.

Key Words: Evans syndrome, Multi-lineage autoimmune cytopenias, Childhood.

A REPORT ON 5 PATIENTS

There is a dearth of detailed descriptions of multi-lineage immune-mediated cytopenias in the medical literature. The presence of autoimmune Coombs’ positive hemolytic anemia, and immune thrombocytopenia in a patient was first described by Evans. Since Evans’ description, neutropenia has also been found to be present in about half of the cases. Previous reports indicate that, multiple-
lineage autoantibodies are directed specifically against red blood cells (RBCs), platelets, or neutrophils and are not cross-reactive\textsuperscript{1}. Among 75 adult and 36 pediatric subjects available for historical review, the clinical course was often characterized by periods of remission followed by recrudescence with fatal outcome\textsuperscript{2-18}. Patients with single-lineage or multilineage antibodies may also have other autoimmune associated phenomena, such as systemic lupus erythematosus (SLE) or other collagen vascular diseases, malignancy, chronic lymphadenopathy, or hypogammaglobulinemia\textsuperscript{16,19-22}. Some of these patients develop other auto-antibodies such as antinuclear antibodies without developing SLE\textsuperscript{17}.

Published reports show that therapy for individuals with multilineage antibody have been diverse but not dissimilar from that utilized for single-lineage autoimmune hematological disease. Specifically, corticosteroid therapy has often been effective in controlling acute episodes; alternatively many patients have required intravenous immunoglobulin (IVIG) to slow the destruction of the targeted hematopoietic cell(s). Disease response to splenectomy is typically short-lived. Other therapeutic modalities have included azathioprine, cyclophosphamide, antithymocyte globulin, actinomycin-C, 6-mercaptopurine or vincristine\textsuperscript{2-5}.

Whether there is indeed a distinction to be made between single and multiple-lineage antibody production is not clear from the available medical literature, particularly with regard to the natural history of the disease or prognosis. To examine this issue, we retrospectively reviewed the clinical course of 50 children up to the age of 18 with chronic single-lineage or multilineage autoimmune cytopenias over a 5 year period. This group included patients with autoimmune hemolytic anemia (AIHA), chronic immune thrombocytopenic purpura (ITP), or autoimmune neutropenia. We studied patients who had multiple-lineage disease to determine whether the natural history of disease in these children was somewhat distinct from that of the group as a whole. We did not study any child whose ITP persisted less than 6 months as such a short course of disease appears to indicate a different disease process and generally produces few, if any, long-term consequences to the child or adolescent.

**PATIENTS and METHODS**

From December 1989 to May 1994, five of 50 patients with chronic immune cytopenias were diagnosed with multi-lineage immune-mediated cytopenias at the University of Texas MD Anderson Cancer Center Division of Pediatrics. Table 1 describes the demographic and the laboratory data at the time of diagnosis. Three patients were Latin American and two were Caucasian; two were girls and three were boys. The median age of the patients at the onset of cytopenia was 7 years (range 3-10 years). The clinical disease courses of these children and adolescents are as follows: Two patients presented with immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA) developed later (patients # 3 and 4). One patient had ITP and immune neutropenia initially and subsequently had a positive Coombs’ test but never developed AIHA. In contrast, laboratory assays for antibodies directed against RBCs, neutrophils and platelets were all positive (patient # 2). One child presented with ITP and immune neutropenia and AIHA developed later (patient # 1). Patient # 5 presented with simultaneous thrombocytopenia and neutropenia but without Coombs’ test positivity. Antineutrophil antibodies were found in blood samples from this patient, but despite the presence of thrombocytopenia, no antiplatelet antibody was detected.

In the three patients with AIHA, the median hemoglobin concentration at the time of initial presentation with hemolytic anemia was 5.8 g/dL (range 5.4-7.8 g/dL). The direct Coombs’ test was positive for IgG and complement (C3) in four patients. The indirect Coombs’ test was positive in two patients. For those five individuals exhibiting thrombocytopenia, the median platelet count was 9000/mm\textsuperscript{3} (range 1-55.000/mm\textsuperscript{3}). The median absolute neutrophil count was 423/mm\textsuperscript{3} (range 352-495/mm\textsuperscript{3}).

**RESULTS**

The clinical data and the treatment given to the five patients are summarized in table 2. Four patients were given primary therapy with IVIG (pa-
tients # 1,3,4,5) and one patient was given prednisone initially (patient # 2). A temporary remission of patient # 2's disease was achieved but in 90 days a relapse occurred. Patient # 2 was then treated with IVIG which led to initial normalization of his blood counts that persisted for 5 months after infusion ceased. Subsequently, the patient's absolute neutrophil count fluctuated between low normal and low. He remained in good health and did not require further treatment.

The clinical courses of the two patients whose disease responded to IVIG are as follows: In patient # 5, a complete and permanent clinical remission of disease was attained, with sustained platelet count and absolute neutrophil count following 2 gm/kg/day of IVIG for 2 days. Patient # 4 received 1 gm/kg IVIG administered for 3 successive weeks. Remission was achieved, but disease recurred. Thereafter, a second remission was achieved with a combination of prednisone (2 mg/kg/d) and IVIG 1 gm/kg/week administered for 3 weeks. The patient subsequently became IVIG independent and IVIG and the steroids were tapered over several weeks. The patient was clinically well and had not received treatment for 4 months at the time of this writing.

Of the two cases that did not respond to IVIG, one responded subsequently to prednisone and complete remission (CR) was attained (patient # 3). In the second patient, hemolysis was ameliorated with concomitant normalization of hemoglobin only after adjunctive treatment with prednisone; however, this patient's thrombocytopenia and neutropenia failed to improve. He therefore underwent splenectomy which resulted in an evanescent increase in his platelet count. He also became transfusion dependent with the exacerbation of his AIHA. Within days, however, he experienced a dramatic decrease in his platelet count (to <10,000/mm$^3$). Further therapeutic management of this patient consisted of sequential doses of intravenous cyclosporin A, oral methotrexate, and protein-A column immunoadsorption with low dose intravenous vincristine. There was no apparent response to any of these modalities. However, several weeks after the last therapy was ceased and four years after diagnosis (six months after splenectomy), the patient demonstrated anti nuclear antibody (ANA) positivity for the first time (he had tested negatively approximately 1-2 times per year during the 4 years since diagnosis). Anticardiolipin IgG antibody was also found to be present. Antibodies to Ro, La, Sm, RNP and double-stranded DNA (dsDNA) were all negative. A diagnosis of SLE was entertained although the patient did not meet the American Rheumatic Association criteria for SLE. At that time, treatment consisting of prednisone given every other day was started. This treatment was initiated for rheumatologic symptoms despite the fact that the patient had failed to show any clinical response to much higher doses of glucocorticoids as recently as 8 months previously. Surprisingly, two weeks after reintro-

### Table 1. Demographic and laboratory data at time of diagnosis in five patients with multilineage autoimmune cytopenias

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Race/sex</th>
<th>Age at onset (years)</th>
<th>Hgb (g/dL)</th>
<th>Coombs’ test</th>
<th>Platelets ($x 10^9$/mm$^3$)</th>
<th>Neutrophils (per mm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LA/M</td>
<td>10</td>
<td>12.4</td>
<td>IgG, C3 +</td>
<td>18</td>
<td>495</td>
</tr>
<tr>
<td>2</td>
<td>C/M</td>
<td>3</td>
<td>13.9</td>
<td>IgG, C3 -</td>
<td>55</td>
<td>352</td>
</tr>
<tr>
<td>3</td>
<td>LA/F</td>
<td>3</td>
<td>7.8</td>
<td>IgG, C3 -</td>
<td>1</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>LA/M</td>
<td>7.5</td>
<td>5.4</td>
<td>IgG, C3 +</td>
<td>9</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>C/F</td>
<td>9</td>
<td>11.0</td>
<td></td>
<td>4</td>
<td>N</td>
</tr>
</tbody>
</table>

**Abbreviations:**
N= Normal; LA= Latin American; C= Caucasian.

$^a$= Patients are listed in chronological order by date of diagnosis.
Table 2. Results of therapy in five patients with multilineage autoimmune cytopenias

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Results after IVIG therapy</th>
<th>Results after corticosteroid therapy</th>
<th>Results after splenectomy</th>
<th>Results after other therapy</th>
<th>Current therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No remission</td>
<td>Remission in AIHA, no response in platelets and neutrophils</td>
<td>Remission, subsequent relapse</td>
<td>CSA, MTX, protein A column immunoadsorption, no response in platelets and neutrophils. Response in Hgb</td>
<td>Prednisone, 30 mg every other day</td>
</tr>
<tr>
<td>2</td>
<td>Remission with increasing frequency of IVIG, remained in remission for 5 mos after IVIG was discontinued. Occasional low neutrophil counts. Off treatment for 4 mos.</td>
<td>Remission, subsequent relapse</td>
<td>Not done</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>No remission</td>
<td>Remission</td>
<td>Not done</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Remission, subsequent relapse continued</td>
<td>Remission, IVIG continued</td>
<td>Not done</td>
<td>None</td>
<td>Of treatment for 5 mos</td>
</tr>
<tr>
<td>5</td>
<td>Remission</td>
<td>None</td>
<td>Not done</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: IVIG= Intravenous immunoglobulin G; AIHA= Autoimmune hemolytic anemia; CSA= Cyclosporin A; MTX= Methotrexate
duction of prednisone therapy, the patient’s plate-let count increased to normal level. His AIHA re-

mained in complete remission. However moderate thrombocytopenia (100,000/mm$^3$) and absolute neutropenia (< 500/mm$^3$) still persisted at the time of this writing.

The median follow-up time for the five patients has been 14 months (range 6-59 months) (Table 3). Patients have experienced a median of two (range 1-3) episodes of hemolytic anemia, a median of one (range 1-4) episode of thrombocyto-

penia and a median of two (range 1-4) episode of neutropenia. No conditions associated with immune cytopenias such as immunodeficiency, malignancy, or chronic lymphadenopathy developed in any of the patients.

**DISCUSSION**

In 1949, Evans and Duane$^6$ described a syndrome in which thrombocytopenia occurred in combination with AIHA. Two of patients in the original study group had neutropenia as well. At that time, the authors ascribed the reduction in all three lineages to a common autoimmune mechanism. However multi-lineage antibody mediated autoimmune disorders can not be defined simply by using the definition that Evans used to descri-

be his patients (each of whom had AIHA and ITP with no definable underlying predisposing condi-

tion). Based on the dearth of subsequent clinical reports and on the large denominators from which the studies cases have been drawn, Evans’ syndrome is rare. In Silverstein & Heck’s series in 1962, the incidence was 0.8% over 8 years (six of the 766 patients had either AIHA or ITP)$^7$. In a more recent report, the rate of incidence was 3.9% over 17 years (seven of the 179 patients with AIHA or ITP)$^8$.

A variety of antibodies directed against RBCs and platelets have been demonstrated in patients with Evans’ syndrome. In 1976, Fagiolo$^9$ reported 32 adult patients with AIHA. The majority of these patients also had antibodies to platelets and leukocytes. The cytopenias in these patients showed different clinical courses and diverse respon-

ses to therapy. No relationship could be demonstrated among the various specificities of red blood cell antibodies, leukocyte antibodies and platelet antibodies. Kakaiya et al.$^{23}$ were among the first to demonstrate in patient with Evans’ syndrome that antibodies against red cells and those against platelets were clearly distinguishable from one another. Pegels et al.$^{11}$ confirmed that autoantibodies in Evans’ syndrome are directed against specific antigens on various blood cells, and they are not cross-reactive$^{11}$.

Autoimmune neutropenia is present in about half of the cases of Evans’ syndrome$^{24}$. Evans described leukopenia in two of his original eight patients$^6$. In Fagiolo’s series, 11 of 16 patients with AIHA had leukopenia although none had ne-

utropenia$^{9}$. Leukocyte antibodies in those pati-

ents were demonstrated by a cytotoxicity test. The presence of thrombocytopenia, neutropenia or both in addition to AIHA is more commonly asso-

ciated with a chronic and relapsing clinical cour-

se$^{25,26}$. Furthermore, many patients may have other associated autoimmune disorders, particular-

ly SLE.

It is hypothesized that genetics play a signifi-

cant role in a person’s predisposition to hematolo-

gic autoimmunity$^{27}$. It was formerly believed that this predisposition was nonspecific; however, re-

sults of recent animal and human studies have shown very specific targets for antibody producti-

on$^{28}$. Because such targeting of autoimmune response is genetically determined by the interac-

tion of major histocompatibility complex (MHC) class II with MHC class I, investigation into these complex interactions may provide insight into why some patients suffer from AIHA while in others, ITP or neutropenia develops. In genetically susceptible individuals, targeting may go beyond RBCs, platelets, and/or neutrophils because antibi-

odies can be directed against many of the com-

ponents of the cell and cell nucleus. It is not pos-

sible to predict when or in whom these additional antibodies will develop. To further complicate this issue, patients with AIHA and/or ITP may develop antinuclear antibodies, circulating immune complexes, and circulating anticoagulants in conjuncti-

on with their immune-mediated cytopenia(s), even if full systemic lupus syndrome never occurs.

During our follow-up of the five drawn from the

group of 50 with chronic autoimmune hematologic disease, we serially assayed for direct Coombs’ test positivity as well as antineutrophil and antiplatelet antibodies. In deciding which cell type was targeted, we made no allowances for the sensitivity and specificity of these tests. In some of our patients, we found antibodies directed to all cell lineages, whereas, in others, we could not detect antibodies to cell lineages that seemed to be clinically affected. The reason for this may be the relative insensitivity of some of the alloantibody tests that have been utilized.

The direct Coombs’ test or direct antiglobulin test is somewhat insensitive to the presence of modest amounts of IgG bound to RBC surface antigens[29]. Conversely, false positive results may occur with cold agglutinins. When immunoblotting or antigen specific assay systems were used, as many as 60-70% of patients with chronic ITP were found to have specific antiGPIIb-IIIa antibodies. An additional 10-20% of the patients had antibody to GPIb[30,31], correlating in a more consistent fashion with the decrement in platelet count.

Assay systems to detect IgG bound to neutrophil antigens have likewise been problematic in producing consistent results. Because of the lack of consistency between and within assay systems, it is prudent to accept that a negative assay does not rule out an autoimmune etiology of neutropenia. This may often cause the researcher to underestimate the presence of multi-lineage autoimmune antibodies. In such a case, it should prove difficult to distinguish inherent pathogenic differences between single-lineage or multilineage disease using currently applied technologies.

To these diagnostic difficulties there is added another complexity: Despite the fact that Evans’ original triad implies an exclusively hematologic autoimmune process, this likely does not adequately characterize the heterogeneous group of conditions that actually constitute multilineage immune-mediated cytopenias. It is possible that the combination of two or more lineages against which autoimmune antibodies are directed may represent a pathogenetic phenomenon that is distinct from autoimmune single-lineage disease. In 1992, Miescher and colleagues[17] reported 10
## Table 4. Summary of literature reports of patients with autoimmune cytopenias

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of pts</th>
<th>Median age at onset</th>
<th>Median nadir Hgb (g/dL)</th>
<th>Median nadir platelets (x10^3/mm^3)</th>
<th>Median nadir neutrophils (x10^3/mm^3)</th>
<th>Treatment employed</th>
<th>Response to treatment</th>
<th>Current treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canpolat</td>
<td>5</td>
<td>24.8</td>
<td>mean given</td>
<td>not given</td>
<td>423</td>
<td>IVG, pred, solenectomy, CSA, MTX, PCA-1a, VCR</td>
<td>3 CR</td>
<td>*</td>
</tr>
<tr>
<td>chin</td>
<td>12</td>
<td>24.8</td>
<td>mean given</td>
<td>not given</td>
<td>423</td>
<td>HD pred, IVG, solenectomy, HD m pred</td>
<td>2 PR (1 on LD pred; 1 no treatment)</td>
<td></td>
</tr>
<tr>
<td>Wang</td>
<td>10</td>
<td>24.8</td>
<td>mean given</td>
<td>not given</td>
<td>300</td>
<td>Pred, solenectomy, IVG, VCR, CPM, Azathioprine, DXM, ATG, plasmapheresis, danazol</td>
<td>6 on LD</td>
<td></td>
</tr>
<tr>
<td>Rackoff</td>
<td>1</td>
<td>6</td>
<td>6.5</td>
<td>10</td>
<td>-</td>
<td>Pred + IVG + solenectomy, m pred (IV), ATG, CSA + pred, HD IVG</td>
<td>7 CR</td>
<td>2 on pred; 1 on danazol</td>
</tr>
<tr>
<td>Petrides</td>
<td>1</td>
<td>18</td>
<td>6.8</td>
<td>25</td>
<td>-</td>
<td>HD IVG</td>
<td>On LD pred</td>
<td></td>
</tr>
<tr>
<td>Oda</td>
<td>1</td>
<td>5.5</td>
<td>6.8</td>
<td>24</td>
<td>-</td>
<td>Pred, HD m pred (IV), CPM, IVG</td>
<td>No treatment, in CR</td>
<td></td>
</tr>
<tr>
<td>Villiger</td>
<td>1</td>
<td>17</td>
<td>9.5</td>
<td>4</td>
<td>-</td>
<td>Pred, plasmapheresis, NR</td>
<td>On monthly IVG, anemia and thrombocytopenia still present</td>
<td></td>
</tr>
</tbody>
</table>

IVG = Intravenous immunoglobulin G; Pred = Prednisone; CSA = Cyclosporin A; MTX = Methotrexate; PCA-1a = Protein column A immunoadsorption; VCR = Vincristine; HD m = Pred = High dose methyl prednisone; CPM = Cyclophosphamide; DXM = Dexamethasone; ATG = Antithymocyte globulin; CR = Complete remission; PR = Partial remission; TR = Transient response; NR = No response; LD = Low dose; HD = High dose; IV = Intravenous; LTFU = Long term follow-up. * = Indicates same patient.
cases with AIHA/ITP or both with various types of additional autoantibodies. These antibodies were directed against antigenic determinants of the cell nucleus, against phospholipids or against various tissue antigens, usually without any clinical consequences. In this report, patient # 1 appears to follow such a clinical course. He did not develop any clinical symptoms of SLE except mild arthralgia. Leddy and Swisher mentioned the occurrence of joint symptoms and Raynaud’s phenomenon in some patients having AIHA with antinuclear antibodies in whom SLE did not develop[32]. The presence of certain autoantibodies, in patients who presented elsewhere with similar clinical and laboratory findings (especially when titers are high, or when the autoantibodies directed against dsDNA), has been found to predict for the development of SLE[33]. Because patient #1 tested had negative test results for anti-dsDNA antibodies and has none of the clinical symptoms for SLE, his disorder may represent a variant of lupus.

The primary reported treatment[2] of Evans’ syndrome is prednisone or another corticosteroid (1 to 2 mg/kg/day). This treatment typically results in a patient’s initial recovery from anemia or thrombocytopenia, but relapses generally occur after the drug dose is tapered or is discontinued[8]. IVIG therapy is also problematic. In a multi-institutional study conducted by Bussel et al.[35], IVIG was administered in a dose of either 0.5 gm/kg/day for five days or 1 gm/kg/day for 5-7 days to a total of 37 patients who had AIHA. The results were combined with those from a review of 36 cases of AIHA treated with IVIG that was reported in the literature. Overall 29 (39.7%) of the 73 cases responded to IVIG therapy. Because of this poor response, the authors concluded that IVIG could not be recommended as standard therapy for AIHA[34]. Based on the observation that free IgG can bind to Fc receptors on macrophages, the same author Bussel selected patients with ITP who were Rh positive and administered anti-D (Rhogam) intravenously[35]. There was a rise in the platelet counts of patients starting 2-4 days after administration. The response time was slightly delayed compared with the response time with IVIG. As with IVIG, the generally accepted mechanism of effect of anti-D has been Fc receptor blockade by substituting antibody-coated RBCs for antibody-coated platelets.

Thrombocytopenia and neutropenia usually respond earlier to IVIG than AIHA does. The presence of an expanded reticuloendothelial system and the larger number of Fc receptors that need to be blocked has been suggested as an explanation for the refractoriness of AIHA. Unfortunately it is not possible to test this hypothesis in such a small number of patients as in our series. To further complicate the interpretation of the clinical responses of these five children, only one patient’s disease remained in continuous remission with IVIG. In the other cases, nonresponsiveness necessitated a switch to steroids or the addition of steroids to the IVIG regimen. As of this writing only one of the five patients has continued to receive long term (prednisone, 30 mg every other day).

This report of five children with multilineage autoimmune disease is one of the few, if not the only, pediatric series providing natural history data. Three of our patients matched the classical definition of Evans’ syndrome. Our retrospective review of the clinical courses of these patients supports the suggestion made by previous authors that multilineage autoimmune disease.

1. Follows a protracted clinical course with frequent relapses.
2. Is often but not invariably associated with other systemic autoimmune processes.
3. Has unpredictable, quite variable and often unsustained responses to therapy.

We could identify no single factor or multiple factors associated with multilineage autoimmune cytopenia that would categorically differentiate the process from chronic single-lineage immune cytopenias such as chronic ITP or AIHA. However, in our series, with so few individuals available for comparison with literature reports of single-lineage disease natural history, such distinction was difficult to make. Yet, despite our inability to draw irrefutable conclusions about clear prognostic differences between single-lineage and multilineage immune cytopenias, we think there are enough
differences to justify a prospective study. The rarity of the syndrome also suggest that a much larger study is necessary. For such a study, we think that any or all of the following hypotheses are worthy of examination:

1. There are genotypic influences (perhaps specific MHC class I and class II differences) that predispose patients to autoimmune cytopenias.

2. These genetic differences will be distinct for individuals with multilineage autoimmune cytopenias compared with those with chronic single-lineage disease.

3. Clinical response to immune suppression therapy and other treatments will correlate with the genetic differences.

4. When other systemic nonhematologic autoimmune disease is present concomitantly, the clinical course of the disease is less predictable, and the patient’s immune response to therapy more variable.

Testing these hypotheses in a large multicenter study may be the only effective course toward understanding the pathogenesis of autoimmune cytopenias and reliably predicting patient’s responses to therapy.

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Address for Correspondence:
Dr. Cengiz CANPOLAT
Marmara Üniversitesi Hastanesi,
Pediatrik Hekotoloji-Onkoloji Bilim Dalı,
Tophanelioğlu Cad. No: 13-15
Koşuyolu-Altunizade
81090, İstanbul, TÜRKİYE