Refractory Idiopathic Immune Thrombocytopenic Purpura in Children
Current and Future Treatment Options

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Abstract

A minority of children with idiopathic or immune thrombocytopenic purpura (ITP) have the refractory chronic form with bleeding problems (stage III or IV). The aim of this article is to provide an update on the immunopathogenesis and management of children with bleeding and severe refractory ITP. The management of such patients, according to a staging guideline, is described.

Recent clinical and laboratory observations document the disturbed immune responses that occur on various levels in chronic ITP. New therapeutic options are directed towards influencing these immunopathogenic mechanisms.

Because ITP is not adequately defined and has heterogeneous manifestations, today’s management recommendations are largely opinion-based rather than evidence-based. In severe refractory childhood ITP, consensus between the treating physician and the patient has to be achieved on an individual basis. The aim is to maintain
Idiopathic immune thrombocytopenic purpura (ITP) manifests as immune-mediated destructive thrombocytopenia. The causative initiating event is still unknown. ITP may be an acute, self-limited, often para- or post-infectious (viral, bacterial, parasitic) disorder. ITP may be a primary chronic autoimmune disorder, or it may develop secondary to a related disease, such as a collagen/endothelial or lymphoproliferative disorder; in the latter case, ITP may be a primary chronic autoimmune disorder, or it may develop secondary to a related disease. From a differential diagnostic viewpoint, alloimmune, neonatal, post-transfusion/post-transplantation, or drug-induced ITP have to be considered.

The incidence of newly diagnosed idiopathic ITP in children is estimated to be four per 100,000 children. The peak age is between 2 and 5 years. Symptoms, signs, and laboratory findings are similar regardless of the form of thrombocytopenic disorder.

A child may be asymptomatic, with thrombocytopenia found during routine blood analysis; however, most children have skin petechiae or purpura, some have mucosal bleeding from the nose, and gastrointestinal or genitourinary tract. Intracranial hemorrhage (ICH) occurs rarely. Symptoms may be exaggerated by certain medications (e.g., aspirin [acetylsalicylic acid]). If ITP is associated with another disease process, symptoms of the primary disease may dominate.

Blood count shows isolated thrombocytopenia with normal hemoglobin/hematocrit levels (unless significant bleeding has occurred), and normal leukocyte differentiation. The mean platelet volume is normal or increased. All other analyses must be within normal range in primary idiopathic ITP.

In a worldwide prospective study of the Intercontinental Childhood ITP Registry, 2031 evaluable children with newly diagnosed idiopathic ITP were enrolled by 136 institutions in 38 countries. The study confirmed the peak occurrence of ITP during spring and a nadir in autumn. The mean age of the children was 5.7 years, and 54.8% were boys and 45.2% were girls. The higher prevalence in boys was observed in all continents. The initial mean age was 6.9 years in children with chronic ITP. Thus, the rate of severe chronic, refractory ITP in children is approximately 4–6%. These children with refractory ITP need special attention.

Before 1980, treatment of children with severe refractory ITP consisted of immunosuppressants (mostly corticosteroids or azathioprine), cytostatics (e.g., vinca alkaloids or cyclophosphamide), or splenectomy. Since immunologic processes in the pathogenesis of ITP, and treatment effects of human immunoglobulin concentrates and Anti-D-Rh0-immunoglobulin have been observed, intensive research and debate on the pathogenesis and treatment of ITP have been ongoing.

The aim of this article is to provide an update on the immunopathogenesis and management of children with severe refractory ITP.

1. Immunopathophysiology of Immune Thrombocytopenic Purpura (ITP)

In response to an antigenic challenge or autoimmune stimulus, the immune system normally produces interaction between antigen-presenting cells and T-lymphocytes (figure 1). T-cell activation and B-cell antibody production occur through signal mechanisms, mainly through cytokines. Regulatory mechanisms, including T-cell and anti-idiotypic antibody responses, downmodulate...
the degree and duration of the immune response of the specific stimulus.

In ITP, the maintenance of self-tolerance and the efficiency of the immune response may be altered in the presence of an antigenic stimulus. In vitro humoral and cell-mediated activation of cytotoxic T cells in patients with ITP have been described.\textsuperscript{10-11} As a consequence of immune activation, increased serum levels of interleukin (IL)-2 have been observed in various autoimmune diseases.\textsuperscript{12-14} In parallel, high levels of IL-10, which is a potent stimulator of human B cells\textsuperscript{15} and downmodulator of inflammatory cytokines,\textsuperscript{16} are detected. Abnormal expression of HLA-DR molecules may mediate the activation of cross-reactive T cells and could lead to autoantibody synthesis.\textsuperscript{17} Chronic ITP may be perpetuated by a constant HLA-DR-stimulated immune response with enhanced cytokine production, by increased activation of T cells, and increased production of specific autoantibodies. Consequently, in patients with ITP, antibody-loaded platelets are prematurely destroyed by opsonophagocytosis of the monocyte-macrophage system, mainly in the spleen.

2. Management of Children with Refractory ITP

2.1 General Aspects

Parents and the child/adolescent with ITP are often worried about bleeding. They are concerned by low platelet counts and perturbed by lifestyle restrictions, including the need to avoid contact sport and certain other activities. On the other hand, the physician, who is confronted with the fears of the patient, knows the relative low risk of severe bleeding, but cannot explain the real origin of the disorder and the individual bleeding risk to the patient. Therefore, it is understandable that a physician might choose to prescribe medical treatment to minimize any risk; however, some experienced hematologists would not give medical treatment to a patient in the absence of bleeding, and would aim to achieve a consensus with the patient/parents and follow a strategy of observation and then intervention only if bleeding occurs or prevention of bleeding is indicated (e.g. if surgery is to be performed).

The literature and internet information on ITP management are mostly opinion-based data and guidelines.\textsuperscript{18,19} There are few evidence-based data;\textsuperscript{20} therefore, in my experience, a staging system of the severity of ITP and management according to the staging can direct the physician to appropriate prescribing behavior and optimize the patient’s quality of life.

2.2 Staging of ITP

Firstly, the severity and bleeding risk of the patient have to be considered. In our clinic, we recommend the staging described in table I.

A patient with stage I or II will only be actively treated in special circumstances. In patients with stage III or IV, the aim of treatment is to reach stage II or stage I.

2.3 Current Treatment in Children with Refractory ITP

If standard treatment (see table II) is ineffective, the following options should be considered (for an overview of medications, adverse effects, and response rate see Berchtold and McMillan,\textsuperscript{20} and Cines and Blanchette\textsuperscript{21}).

2.3.1 Vinca Alkaloids

Vincristine or vinblastine produce lymphocytopenia.\textsuperscript{20,21} An IV dosage of vincristine 1.5 mg/m\textsuperscript{2}, maximum 2mg, or vinblastine 0.1 mg/kg bodyweight is given every 7 days for 4–6 weeks. In our clinic we add corticosteroids (2 mg/kg bodyweight orally in two doses per day) during the first three days after each IV dose of vincristine or vinblastine. Long-lasting remission of ITP is seldom observed.
is indicated if Stage II or I of ITP (table I) is not reached after medical treatment is given for 2–4 months and disturbing adverse effects occur, or if a life-threatening bleeding episode has been observed in an individual child with chronic ITP.

### 2.3.6 Plasmapheresis or Protein A Immunoadsorption

Plasmapheresis or protein A immunoadsorption transiently reduces (auto)antibodies and platelet activation. The response rate is low and the costs are high. In children, this procedure is indicated in those with high platelet-associated antibody levels and severe bleeding. Other treatment options (e.g. dapsone therapy) have not shown convincing results in ITP.

### 3. Recent Developments and Possible Future Treatment Options for Refractory ITP

Children with stage III or IV ITP (see table I) may benefit from new therapeutic developments, with the main goal being to influence the alterations in immune response that are associated with ITP (see section I).

#### Table II. Treatment options in immune thrombocytopenic purpura (ITP)

<table>
<thead>
<tr>
<th>Standard treatment of chronic ITP</th>
<th>Current treatment of refractory ITP</th>
</tr>
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<tbody>
<tr>
<td>Immunoglobulin: IV 0.4 g/kg bodyweight once every 2–8 weeks</td>
<td>Plasmapheresis or protein A immunoadsorption</td>
</tr>
<tr>
<td>Anti-D-RhO-immunoglobulin: IV 0.5 μg/kg bodyweight per dose; maximum every 14 days</td>
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<tr>
<td>Low dose corticosteroids: oral 0.1–0.4 mg/kg bodyweight per day</td>
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<tr>
<td>Cyclic high-dose corticosteroids</td>
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<tr>
<td>Splenectomy</td>
<td></td>
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<tr>
<td>Plasmapheresis or protein A immunoadsorption</td>
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#### 2.3.2 Azathioprine

Azathioprine is given in a dosage of 1–4 mg/kg bodyweight per day orally. The drug causes leukopenia. Azathioprine should be given for at least 4 months, but no longer than 12 months. The response rate is approximately 30% within 6–8 weeks.

#### 2.3.3 Cyclophosphamide

Cyclophosphamide is effective in 30–40% of patients and is given orally at 1–2 mg/kg bodyweight per day. If a response occurs within 2 months, the treatment should be continued for a total of 3 months and then stopped. The mild leukopenia/lymphopenia caused by the drug is tolerable. High fluid intake to prevent hemorrhagic cystitis is important.

#### 2.3.4 Cyclic High-Dose Methyprednisolone

Cyclic high-dose methylprednisolone (IV 20–30 mg/kg bodyweight) or dexamethasone (oral 1 mg/kg bodyweight) can be given on 3–4 consecutive days every 4 weeks for 4 months. However, both the adverse effects and response rates of these high-dose corticosteroid regimens are disappointing in children.

#### 2.3.5 Splenectomy

Splenectomy, performed either traditionally or by laparoscopy, has a 70% immediate remission rate. In children <5 years of age, early splenectomy should be avoided because of the risk of post-splenectomy sepsis. Pneumococcal, haemophilus, and meningococcal vaccinations prior to splenectomy, and long-term prophylactic antibiotics afterwards, are indicated. Splenectomy
3. Treatment Influencing Antigenemia

Platelet counts were improved after antibacterial eradication of *Helicobacter pylori* and a positive urea breath test for *H. pylori* associated with gastritis or peptic ulcer disease in patients with chronic ITP.[37,28] This observation of reduction of antigenemia may be a model of long-term downregulation of the upregulated immune response to antigens.

Downmodulation of antigenemia may also be the reason for the improvement that is seen during antiviral treatment in patients with HIV-related thrombocytopenia.[29] In children with postinfectious (acute) ITP, the disappearance of antigenemia during immune recovery may resolve thrombocytopenia.

3.2 Treatment Influencing the T-Cell Immune Response

3.2.1 Cyclosporine

In child or adult patients with normal renal function and refractory severe ITP (stage III or IV), cyclosporine causes a dose-dependent increase in platelet count.[30-32] The dose of cyclosporine should be adjusted according to the serum level and with the aim of achieving a safe thrombocyte count (induction of stage II or stage I ITP [see table II]). This way, low-dose cyclosporine treatment with less adverse effects may be possible.[30-32] In one study, the long-term response rate in refractory idiopathic ITP was 11 out of 20 patients (five complete response, six partial response) after discontinuation of treatment.[32] No large study exists.

3.2.2 CTLA-4-Ig

CTLA-4-Ig, a fusion protein between CTLA-4 and the immunoglobulin Fc portion, aims to block T-cell co-stimulation.[33] This treatment was successfully used in patients with psoriasis. Such a drug may also be effective in other autoimmune disorders that are driven by dysregulated T cells, including ITP, but no data are yet available.

3.3 Treatment Influencing the B-Cell Immune Response

3.3.1 Anti-CD20 Monoclonal Antibody (Rituximab)

The human/mouse anti-B-cell monoclonal antibody, rituximab, is a κ-immunoglobulin with murine light and heavy chain variable sequences and human constant sequences.[34] The chimeric molecule binds to the CD20 antigen on B cells, and mediates its lysis by immune effector cells. Among other autoantibody-producing disorders, refractory ITP and Evans syndrome benefit from rituximab (table III).[35] Within three to four courses of rituximab (IV 375 mg/m²/week × four weeks), approximately two-thirds of patients had an increase in platelet count and some had long-lasting responses (>6 months). Adverse events during treatment were transient and mild, and comprised fever, chill, headache, dizziness, asthenia, nausea, vomiting, and hypotension. No infections were noted. Dose-finding studies are needed in this possible indication of rituximab.

3.3.2 Anti-CD52 Monoclonal Antibody (Alemtuzumab)

CD52 antigen is present on lymphocytes and monocytes.[49,50] Monoclonal antibody directed against CD52 (alemtuzumab) is effective in clearing B lymphocytes in patients with B-cell chronic lymphocytic leukemia, as well as in patients with vasculitis[51] or Wegener’s granulomatosis.[52] Fifteen out of 21 children and adults with hemolytic anemia, pure red cell aplasia, ITP, or Evans syndrome showed a response to treatment with alemtuzumab; some patients had a sustained response.[53] Adverse effects during treatment included fever and chill. Serious adverse effects can potentially occur with alemtuzumab, such as profound lymphocytopenia (with potential for opportunistic infection), IV hemolysis, systemic venous thrombosis, or thrombotic thrombocytopenic purpura. Alemtuzumab may be indicated in severe refractory ITP with life-threatening episodes.
3.3.3 Interferon-α-

Uncontrolled studies of interferon-α2a\(^{54,55}\) showed a response rate of 25% in children and adults with chronic ITP. However, it may not be feasible to conduct the essential controlled trials that are needed to establish the efficacy of interferon in ITP because the drug is associated with significant adverse effects, a difficult mode of application (300 000IU intramuscularly three times weekly for 4 weeks) and is expensive.

3.4 Other Options

Thrombopoietin may be effective in those patients with ITP and megakaryocyte involvement (depletion by specific antibodies). Initial data have shown favorable responses in adults.\(^{56}\)

3.4.1 Autologous Hematologic Stem Cell Transplantation

Twelve adult patients with severe refractory ITP underwent autologous hematologic stem cell transplantation.\(^{57}\) Four patients achieved complete remission, and two patients achieved partial remission. This approach must be considered experimental.

4. Conclusions

The management and treatment of children with chronic refractory ITP depends on the severity of bleeding. The proposed ITP staging guideline (based on the experience of the author) may lead to minimal therapeutic intervention by the physician, and may encourage more biologic-oriented intervention for chronic refractory ITP.

Over time, children with ITP and their parents become experienced in creating a good quality of life, despite some behavioral/lifestyle restrictions. If the disease cannot be maintained in stage I or II with this approach, a more aggressive interventional management strategy has to be chosen (splenectomy, cytotoxic drugs and combinations, experimental treatment).

There is presently a paucity of data on the newer treatments in children with refractory ITP. In 1997, the Intercontinental Childhood ITP Study Group (ICIS)\(^{58}\) started to perform prospective cooperative registries and studies (e.g. splenectomy registry, registry on bleeding symptoms) as a basis for future controlled studies of specific medical interventions in a clearly selected patient subpopulation with ITP. These studies are expected to provide useful information to guide the management of pediatric patients with ITP in the future.

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