Reassessment of treatment modalities for paediatric patients with chronic immune thrombocytopenia

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Keywords
Immune thrombocytopenia, splenectomy, rituximab, children

Summary
Approximately 70% of children have the acute form of immune thrombocytopenia (ITP), which is defined by recovery within six months of presentation with or without treatment. Chronic ITP is to be reserved for patients with platelets < 100 000/μl for more than twelve months and exclusion of other diagnosis like systemic lupus erythematosus or bone marrow failures. In children, the chance of spontaneous recovery is 52% after diagnosis of chronic ITP. The Intercontinental Childhood ITP Study Group recommends that children without bleeding may not require therapy regardless of their platelet count. Whereas in patients with bleeding symptoms first line therapy is defined and includes steroids or immunoglobuline, second line therapy in refractory patients with significant hemorrhagic problems is unclear. Guidelines recommend splenectomy, but for more than 50 years patients and physicians look for pharmacological alternatives. It may be that rituximab is a promising option which has been proven to be effective with few adverse effects. Till now the treatment has focused on immunomodulation. Research has now focused on stimulating platelet production. In this review we discuss old and new therapy modalities for children with cITP.

Immune or idiopathic thrombocytopenic purpura (ITP) is one of the most common causes of symptomatic thrombocytopenia in children. The Intercontinental Childhood ITP Study group recommends to prefer the term „immune“ instead of „idiopathic“, to emphasize the immune-mediated mechanism of the disease and to choose „primary“ to indicate the absence of any obvious initiating and/or underlying cause (51). The incidence of ITP is estimated to be between three and eight cases per 100 000 children. Children with ITP usually present between two and ten years of age, with a peak incidence between two and five years (11, 35, 36, 63). Half of the patients were between one and four years of age and about 80% below eight years of age.

In ITP, IgG-autoantibodies are directed against platelet membrane antigens, such as glycoprotein complex IIb/IIIa (1, 18). The antibody-coated platelets have a shortened half-life because of accelerated clearance by tissue macrophages in the spleen and other portions of the reticuloendothelial system. In some patients with chronic ITP, antibodies are not demonstrable and an alternative mechanism of T-cell-mediated cytotoxicity may cause platelet destruction. The cytokine pattern of lymphocytes seen in patients with chronic ITP suggests an early CD4+ Th0 and Th1 cell activation (53). This occurs more commonly in adults with ITP than in children.

In about 60% of paediatric patients, there is a history of a prior infection (35). An increased risk of ITP is also associated with measles-mumps-rubella (MMR) immunization (23, 30, 42). Approximately 70% of children have the acute form of ITP, which is defined by recovery within six months of presentation with or without treatment (52). Pharmacologic intervention, when used, is directed toward the early control of symptoms, such as stopping severe hemorrhage or...
minimizing the risk of significant bleeding. Such therapy does not affect the long-term outcome. Early treatment accelerated platelet recovery in patients with acute ITP, but did not reduce the risk of developing chronic ITP or morbidity (58).

**ITP**

**Persistent ITP**

“Persistent ITP” is introduced for patients with ITP to define the period lasting between three and twelve months from diagnosis. This category includes patients not achieving spontaneous remission or not maintaining their response after stopping treatment (11).

Vranou et al. reported a frequency of ITP in 6.0% of their patients. The median age of patients at the onset of the disease was 50 months and the median time interval elapsed from the first presentation of ITP to recovery was 19.5 months (percentiles 25th–75th: 11.75–42.7 months). 2/3 of the children had one recurrence, 20% had two recurrences, and 10% had three to four recurrences. The duration of each thrombocytopenic episode varied from patient to patient and from episode to episode in the same patient. Most of the thrombocytopenic episodes had a short course; however, around 23% of them appeared with a course of more than six months (59).

**Chronic ITP**

The term chronic ITP is to be reserved for patients with ITP lasting for more than twelve months (51). Although the presentation of chronic and acute ITP are similar, children who have chronic ITP are more likely at presentation to have an insidious onset of symptoms, be older, and not have a history of a prior infection or vaccination before presentation (25).

Individuals with chronic ITP should undergo evaluation to exclude other causes of thrombocytopenia, such as chronic infections (including HIV, CMV), bone marrow failure (Fanconi anemia, myelodysplastic syndrome), collagen vascular disorders (systemic Lupus erythematosus), von Willebrand disease type 2B, thrombotic thrombocytopenic purpura, Evans syndrome and other autoimmune or immunodeficiency disorders (common variable immunodeficiency, Wiskott-Aldrich syndrome).

Management of children with chronic ITP should focus on minimizing the individual’s risk for bleeding. The goal of treatment in persistent or chronic ITP is less well defined. Decisions based solely on the platelet count remains controversial. While most guidelines suggest that treatment should be considered with counts less than 30 000/μl in adults, the Intercontinental Childhood ITP Study (ICIS) group recommended that children without bleeding may not require therapy regardless of their platelet count, with the exception of on demand therapy (51). In chronic ITP, platelet counts tend to range between 20 000 and 75 000/μl; consequently, many patients will require no treatment (40). It is uncommon for an individual with chronic ITP to have a platelet count less than 10 000/μl (39).

**Treatment options**

A small percentage of patients with chronic ITP will have persistent significant hemorrhagic symptoms and require repeated, sometimes almost continuous, pharmacologic treatments. For such patients, the risks and benefits of splenectomy must be considered.

**First line therapy**

**Glucocorticoids**

The mechanism of action of corticosteroids in ITP is still obscure, although they act through several mechanisms including inhibition of phagocytosis and antibody production, improved platelet production and increased endothelial stability (26, 33). The dose and the type of corticosteroids in the management of ITP is not clear as several regimens of prednisolone and methylprednisolone dosage have been used (8, 10, 12, 17).

Most experiences were done in acute ITP. The side effects of steroid therapy include cushingoid facies, weight gain, fluid retention, acne, hyperglycaemia, hypertension, mood changes, avascular necrosis and osteoporosis. Toxicity is related to the dose and duration of therapy.

**High-dose dexamethasone**

Andersen et al. reported on the use of high-dose dexamethasone in ten adult patients with cITP. These patients had received multiple therapies including splenectomy. A sustained response rate of 100% was reported (3). These promising results have not been reproduced in children with cITP. Review of the published case series suggests that a minority of pediatric patients do have a durable response to the short-pulse, high-dose dexamethasone treatment, but most of the children had major side effects (10, 12, 17).

**Immunoglobulin**

The original postulate is that the beneficial effect of intravenous immunoglobulin (IVIG) in ITP is a transient impairment of reticuloendothelial clearance function, also referred to as macrophage “blockade” mechanism (19, 38). Other immunomodulatory effects of IVIG include inhibition of complement binding to platelets, interference of immune complexes binding to platelets, immune activity of antiidiotype antibodies, and impaired release of pro-inflammatory cytokines from monocytes (38).

**IVIG**

IVIG is effective in elevating the platelet count in approximately 80% of patients. Platelet counts may begin to increase after one day and usually reach peak levels within one week after treatment (Tab. 1). Several reports document the success in temporary platelet count elevation with pooled immunoglobulin in cITP. However, response is generally transient, lasting no longer than 3–4 weeks, after which the platelet counts decrease to pre-treatment levels (14, 29).

In addition, the acute adverse effects of IVIG treatment are not negligible. The more common side effects of fever, flushing, and headache may be debilitating for one to three days after infusion. Rarely, aseptic meningitis may occur. Pooled immunoglobulin products have the risk of transmission of infectious agents.
Anti-D immunoglobulin

Anti-D is a plasma-derived, hyperimmune immunoglobulin with high-titer of anti-D antibody. It can only be used to treat Rh (D) positive patients with ITP. The presumed mechanism of action is phagocytic cell blockade. Patients with intact spleen respond better than splenectomised patients. Anti-D use in cITP showed that most patients experienced a significant rise in platelet concentration (4, 20). The broad experience of anti-D use in cITP suggests that this agent may be used successfully to defer splenectomy in childhood cITP, as reported by Andrew et al. in 88% of patients (4).

Fever and headache are not uncommon, but are short lived adverse effects and can be prevented or ameliorated in most cases with antipyretic medication. The shorter, 5- to 30-minute infusion time and lower cost relative to IVIG treatment make anti-D an attractive alternative for the treatment. The expected extra vascular haemolysis is usually mild, with clinically significant drops in haemoglobin levels. In the study of El Alfy, the Hb drop caused by intravascular haemolysis was detected in 61% of patients on day 3 and in 78% patients on day 7, with Hb decreases of 0.4–3.0 g/dl and a reticulocytosis. All patients recovered spontaneously and achieved the pre-treatment Hb levels within 3–4 weeks after infusion (20).

The relatively small plasma donor pool used in the isolation of anti-D theoretically lessens the likelihood of infectious disease transmission. Until the unresolved issues surrounding BSE and other agents are reconciled, any therapeutic blood derivative will pose at least a theoretical risk of infection transmission.

Second line therapy

Neunert et al. designed a survey of members of the American Society of Pediatric Hematology-Oncology (ASPHO). They described a 5-year-old female with ITP for one year who was unresponsive to steroids, IVIG, and anti-D immunoglobulin and having frequent episodics causing interference with her daily activities. 33% of respondents stated that they would recommend splenectomy for such a child and 67% recommended a treatment with rituximab. If initial drug therapy failed, 47% would proceed with splenectomy (43).

Splenectomy

The long lasting response rate in children is similar or even superior to that in adults (7, 34). Yet, the risk benefit ratio of splenectomy in children is less favourable than in adults. In children, the risk of splenectomy, especially with respect to post-splenectomy sepsis is appreciable (3%). Moreover, in children, the chance of spontaneous recovery is 52% of which 2/3 within three years after diagnosis of chronic ITP (5).

Splenectomy is effective in improving the platelet count and reducing the associated risk of bleeding in 60 to 90% of children with chronic ITP (37). No universally accepted standards for the timing of splenectomy in chronic ITP exist, but the American Society of Hematology guidelines reserve splenectomy for children ages 3–12 years with disease duration > 12 months who have bleeding symptoms and a platelet count of < 10 000/μl. For children older than eight years of age, the guidelines include a platelet count of 10 000–30 000/μl. Similarly, guidelines from the British Committee for Standards in Haematology reserves splenectomy for children with persistent disease for 12–24 months with life-threatening hemorrhage and children with chronic severe unrelenting disease with impaired quality of life. Both sets of guidelines are based on opinion rather than on firm evidence (1, 24).

After splenectomy, the time to assess the response in terms of platelet count should be within 1–2 months from surgery and off any treatment. Approximately 25 to 30% of children with chronic ITP have ongoing hemorrhagic problems after splenectomy. In these cases, evaluation should identify any possible accessory spleen, which should be removed, if present. Only one trial, however, specified a follow-up period of at least four years and reported a substantially lower response rate compared with that after one year (6).

In addition, infection prophylaxis before and after splenectomy is essential. This issue demands a comprehensive investigation, as the rate of penicillin-resistant pneumocococcus increases. The risk for serious post splenectomy infection is greater in children younger than five years, who are therefore treated with prophylactic penicillin after splenectomy. Although there are no data on the efficacy of vaccination against encapsulated bacteria (Streptococcus pneumoniae, Haemophilus influenzae B, and Neisseria meningitides). However, the prophylactic immunisation is generally advised at least two weeks before splenectomy.

An older study found that 6% of patients experienced a spontaneous remission three to six years after diagnosis. Splenectomy failure, acute and late morbidity after splenectomy, the low rate of mortality of cITP itself, and the chance of late spontaneous remission of thrombocytopenia may lead physicians and patients to defer splenectomy indefinitely in childhood cITP (60). However, still 15–20% of the patients with chronic ITP are splenectomized and ways to prevent or postpone splenectomy should be considered (5, 7)

Rituximab

Rituximab is a chimeric humanised monoclonal antibody (49) first developed for the

Tab. 1 Current pharmacological treatment of cITP in children; adapted from (51)

<table>
<thead>
<tr>
<th>treatment</th>
<th>dose range</th>
<th>duration/frequency</th>
<th>time to response (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>initial</td>
</tr>
<tr>
<td>prednisone</td>
<td>0.25–4 mg/kg</td>
<td>4 d – 4 w</td>
<td>4–14</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>20–25 mg/m² or 40 mg absolute</td>
<td>4 d/2 – 4 w</td>
<td>2–14</td>
</tr>
<tr>
<td>IVIG</td>
<td>0.25–2 g/kg</td>
<td>1 – 5 d</td>
<td>1–3</td>
</tr>
<tr>
<td>anti-D</td>
<td>25–75 μg/kg</td>
<td>1 d/1 – 5 w</td>
<td>1–3</td>
</tr>
<tr>
<td>rituximab</td>
<td>375 mg/m²</td>
<td>1 d/1 – 4 w</td>
<td>7–56</td>
</tr>
</tbody>
</table>

d: day; w: week

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Hämostaseologie 2/2009
treatment of adult B-cell non-Hodgkin lymphoma, but several studies have now shown that it may also be effective in autoimmune diseases like ITP (54). It targets the CD20 antigen on the surface of normal and malignant mature and mature B lymphocytes, and induces B cell destruction by means of both complement mediated lyses and antibody-dependent cellular cytotoxicity. Induction of apoptosis has also been demonstrated (2, 22).

Most of the mature B-cells (plasma cells) do not express CD20 on their surface. However, B-cell depletion occurs in up to 6–12 months. Moreover, immunoglobulin levels in most patients remain unchanged, though re-duction or disappearance of auto-antibodies have been demonstrated.

Additional proposed mechanisms include Fc-receptor blockade of the macrophages. This mechanism is similar to that supposed to be involved in the therapeutic mechanism of IVIG and may explain the prompt effect that can be seen after rituximab administration.

In addition Stasi et al. could demonstrate, that B-cell depletion induced by rituximab can revert the abnormalities of the T-cell compartment in patients with ITP who respond to treatment (53).

Rituximab may be useful in treating both primary and secondary refractory chronic ITP in children (32, 45, 57, 61). In an open label study of 36 children who received a weekly intravenous dose of 375 mg/m² rituximab for four doses, it improved the platelet count to more than 50,000/µl in 33–42% of the children (9, 46). Others have observed a similar response rate using a single dose of rituximab (56). The median time to platelet counts > 50,000/µl was one week (range one to seven weeks) (9).

Immediate side effects that are reported include chills, fever, pruritus, urticaria, and throat tightness and were seen in up to 17% of the patients; 12% of the children have signs of serum sickness which may be a reason to dis-continue the treatment (9, 61). Despite the B-cell depletion and decreased levels of immunoglobulins in some children, no in-creased frequency or severity of infections was noted (9, 46, 61). However, two adult pa-tients have died after being treated with ri-tuximab for systemic lupus erythematosus (SLE). The cause of death was a viral infection of the brain called progressive multifocal leukoencephalopathy (PML) that is caused by reactivated JCV virus. The incidence of JCV virus is around 50% in children up to five years and about 80% of children older then ten years. Rituximab is only licensed for the treatment of CD20 positive non-Hodgkin lymphoma and rheumatoid arthritis.

Third line therapy

For those refractory patients with significant hemorrhagic problems who fail trials of steroids, IVIG and anti-D Ig, the use of various agents such as danazol, interferon, cyclospo-rine, cyclophosphamide, vinca alkaloids, azathioprine and mycophenolate mofetil, alone or in combinations has been suggested, based primarily upon observational studies in adults (55). Data are limited in children. Responses with these agents do not usually exceed 30–35% and, if seen, they may only be apparent after several weeks. The toxicities as-sociated with these agents should be carefully evaluated when further treatment is required.

Danazol

Danazol is a synthetic steroid derived from ethisterone approved for use in the treatment of endometriosis and fibrocystic breast dis-ease. Temporary platelet count elevation has been reported in the majority of adults with cITP receiving 50–800 mg of danazol daily for two months. Some adults with cITP experienced years of unmaintained remission after long-term therapy (> 2 years) (41). The pediatric experience with danazol for cITP is not as well described. However, Weinblatt et al. de-scribed a favourable response in five of ten children. (62). Responses occur slowly and therefore treatment should be continued for at least three to six months. Known adverse ef-fects are mostly reversible. They include hepato-toxicity, virilisation, lethargy, amenorrhoea in women, rash and weight gain, but may deter the use of danazol in paediatric cITP.

Cyclosporine A

Cyclosporine suppresses the T-cell function, inhibits antigen-induced activation of CD4+ T lymphocytes and the production of inter-leukin-2 and other cytokines. Complete re sponses are seen in 30 to 40% of patients (21, 31, 47). The majority of the patients experi enced adverse effects, most frequently hypertension, muscle pain, increased creatinine, and headache. Patients on high doses (5–6 mg/kg/day) discontinued treatment due to the adverse effects more often than those with lower doses (2.5 to 3 mg/kg/day) (21, 31, 47).

Mycophenolate

Mycophenolate mofetil (MMF) is a newer immunosuppressive medication, which has been used successfully with acceptable toxicity in solid organ transplants patients to reduce the risk of organ rejection. Additionally, it is used as second line treatment in several autoimmune diseases.

Studies showed that MMF results in 24 to 33% complete responses, lasting from two to more than 13 months. The adverse effects were mild and reversible (nausea, diarrhoea, headache, and backache) (27, 48). MMF may be a useful component of a combi-nation protocol but does not appear to be highly effective as sole therapy in patients with refractory ITP (48).

Platelet transfusions

Platelet transfusions are indicated only for intracranial hemorrhage or life threatening hemorrhage. Monitoring of the increment in platelet count should be used. Other modalities of treatment such as steroids and IVIG should be given at the same time. Platelet transfusion should not be used for simple thrombocytopenia.

Future therapy

Till now the treatment has focused on suppressing the anti-platelet antibody production or blocking the destruction of antibody-coated platelets. Research has now focused on stimulating platelet production with new molecules, which bear no structural resem-bliance to thrombopoietin, but still activate the TPO receptor. Studies have been completed for two TPO mimetics, Romiplostim (AMG 531) and Eltrombopag (SB–497115) (50).

Romiplostim is a recombinant protein. It is administered subcutaneously once weekly. The preliminary results are promising in adult ITP patients. The analysis indicates that
they had a stable mean platelet count of greater than 100,000/μl, were on a stable weekly dose, and half were able to stop other concomitant immunosuppressive drugs. The most frequently reported complication of therapy was mild headache; in eight patients there was a mild-to-moderate increase in bone marrow reticulin but without collagen fibrosis and with normal cytogenetic findings (15, 16, 44). In a long-term study with treatment up to 156 weeks in 142 adult patients adverse events were mild or moderate in severity. During the study, one patient transiently developed neutralizing antibodies against romiplostim but not worsened thrombocytopenia. These antibodies showed no cross activity against thrombopoietin, because of absence of amino acid sequence homology. Thrombotic or thromboembolic events were reported in nearly 5% of patients (16).

Eltrombopag is a small hydrazine organic compound. It is given orally once daily. In a placebo-controlled phase 2 trial, platelet responses were observed in 70–80% of the adult patients. No significant adverse events were seen (13).

Conclusions

ITP remains a diagnosis of exclusion. The diagnosis of chronic ITP should be given to patients with thrombocytes <100,000/μl for more than twelve months and absence of other illness. The risk of severe bleeding is low; treatment in children is generally not indicated except for patients with recurrent severe bleeding.

The availability of multiple treatment options underlines the lack of consensus in the management of childhood chronic ITP. Treatment of childhood cITP should be individualized taking into account the:

- natural history of the disease with spontaneous remissions after years,
- medical effects and possible adverse effects and
- social history of the patient and family.

First line treatment options remain corticosteroids and immunoglobulins. Splenectomy may be an effective option for patients who are refractory or have multiple relapse after first line therapy. But this therapy options have been discussed for more than 50 years because of its invasive procedure with possible side effects like infections. Rituximab is a promising therapy option which has been proven to be effective with few adverse effects. Although large trials are lacking, rituximab seems an attractive, albeit expensive, alternative for splenectomy.

Most third line options are more or less experimental, with many adverse effects and limited or poorly studied therapeutic value in paediatric patients. Low-dose cyclosporine and mycophenolate mofetil seem effective alternatives in refractory adult patients. Only few data are available in paediatric patients.

References