Netherlands
The Journal of Medicine

REVIEW

Chronic idiopathic thrombocytopenic purpura: present strategy, guidelines and new insights

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ABSTRACT

Idiopathic thrombocytopenic purpura (ITP) is an immune-mediated thrombocytopenia. The diagnosis is made after exclusion of other secondary causes of thrombocytopenic disorders. The primary treatment goal is to prevent severe bleeding rather than achieve normal platelet counts. In adults ITP usually has an insidious onset and chronic course. Although ITP is a relatively common haematological disorder, there are important unresolved issues in its management, especially for chronic refractory ITP patients. New therapeutic agents have changed strategies for ITP treatment. This article reviews the treatment indications and options of chronic ITP in adults in the literature and compares them with the treatment indications and treatment options used by the Dutch internist.

KEYWORDS

Chronic, idiopathic thrombocytopenic purpura, present strategy, treatment overview

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) was first described by P.G. Werlhof in 1735 as 'Morbus Maculosus Hemorrhagicus.[1] The disease is characterised by premature destruction of autoantibody-coated platelets, causing thrombocytopenia and subsequent mucocutaneous bleeding.

In children the onset is typically abrupt, and the course is usually self-limiting, requiring only supportive management. ITP in adults often has a more persistent course; it may last for many years and is characterised by recurrent relapses, frequently requiring medical intervention.

Since Harrington's studies more than 50 years ago, the pathophysiology of the disease is known to be immune-mediated.[1] Harrington developed severe transient thrombocytopenia after injecting himself with plasma from chronic ITP patients.

ITP is the result of accelerated platelet destruction by the reticuloendothelial system, primarily the spleen.[2,3] Although the main problem in ITP is increased platelet destruction, studies in the 1980s showed that megakaryocyte maturation and platelet production in some chronic ITP patients are also impaired, possibly due to megakaryocyte-reactive autoantibodies.[4] Low platelet counts in ITP patients may therefore be the result of both increased platelet destruction and a decreased platelet production.

ITP remains a diagnosis made after exclusion of other causes of thrombocytopenia (e.g. multisystem autoimmune diseases, lymphoproliferative disease, drug-induced thrombocytopenia, infections, and myelodysplastic syndromes). Although there are techniques available to measure antibodies with glycoprotein IIb/IIIa and Ib/IX, IV and V specificity, both platelet-associated and free in the plasma, the lack of sufficient sensitivity makes them of little diagnostic value.[2,3,5,6] The diagnosis of ITP is based principally on the patient's history, findings during physical examination, complete blood count and peripheral smear, which should exclude other causes of thrombocytopenia (*table 1*).[6-8] Bone marrow examination is recommended in adults with atypical features at diagnosis or in those >60 years and in patients scheduled for splenectomy.

Table 1. *Diagnostic criteria for ITP*

History
Bleeding symptoms (type, severity, and duration of bleeding)
Systemic symptoms (weight loss, fever, headache, and symptoms of autoimmune disorders)
Risk factors for HIV infection
Pregnancy status
Medication (heparin, alcohol, quinine, sulphonamides, aspirin)
Family history
Physical examination
Bleeding signs
Liver, spleen, lymph nodes, and jaundice
Evidence of infection, autoimmune disease, and thrombosis
Isolated thrombocytopenia (low platelet count with an otherwise normal complete blood count and blood smear)
Exclusion of pseudothrombocytopenia (EDTA artefact)
Absence of
Other autoimmune diseases
Disseminated intravascular coagulation
Drug-induced thrombocytopenia
HIV infection
Lymphoproliferative disorders
Myelodysplasia
Agammaglobulinaemia
Allo immune, congenital or hereditary thrombocytopenia

No firm data on incidence and prevalence are available, although ITP seems to be a relatively common haematological disorder. Estimations on incidence for adults in the US and UK are about 60 per million per year.[6] In adults ITP occurs 1.7 times more among women than in men.[9] The median age at presentation is 38 to 49 years and the incidence increases with age.[9,10]

In this review we summarise the treatment strategies for chronic ITP in adults and report the present therapy strategy among Dutch internists.

METHODS

For the literature review, we searched Medline via PubMed using the following criteria: 'autoimmune thrombocytopenic purpura', 'ITP', 'idiopathic thrombocytopenic purpura', 'immune thrombocytopenic purpura', 'ITP + treatment', 'autoimmune thrombocytopenic purpura + treatment', 'ITP + steroid', 'intravenous immunoglobulin + ITP', 'ITP + anti-D'. 'ITP + splenectomy', 'ITP + danazol, 'ITP + vinca alkaloids, 'ITP + cyclophosphamide', 'ITP + cyclosporine', 'ITP + dapsone', 'ITP + Helicobacter pylori', 'ITP + stem cell transplantation', 'ITP + chemotherapy', 'ITP + mycophenolate mofetil' and 'ITP + anti-CD20 antibody'.

RESULTS OF LITERATURE REVIEW

Indications for treatment

Since 21% of ITP patients are asymptomatic at diagnosis, it is important to establish criteria for timing the initial treatment, because of the increased frequency of discovering asymptomatic patients (21% of the ITP patients.[10] In view of the possible adverse effects of treatment, and the unpredictable and frequently transient outcomes, caution is recommended.[11]

Several studies have shown that ITP patients with platelet counts persistently <30 x 10^9/l are at risk of a life-threatening bleed.[10,12]

In general, most doctors decide to start treatment when platelet counts fall below this threshold.[8,13] Starting treatment when platelet counts are between 30 and 50 x 10^9/l may be appropriate in patients at higher risk of haemorrhage due to lifestyle, concomitant medications, hypertension, any scheduled surgery, or head trauma.[14,15]

Emergency treatment

Hospitalisation should be considered for patients with extremely low platelet counts (<5 x 10^9/l) and/or significant bleeding. The main goal is to increase the platelets to safe levels and immediately stop the bleeding. The treatment generally consists of intravenous immunoglobulin (1.0 g/kg/day for two days),[16] prednisone (1.0 g/kg/day iv for three days) or a combination of both.[13] Combination therapy is preferred if a swift increase in platelet count is warranted.[17] In cases of severe haemorrhage, platelet transfusions may be necessary,[6,7] although the survival time of transfused platelets is short.

Initial treatment

Steroids

Oral prednisone is the generally accepted strategy of choice for ITP patients who require treatment. The therapeutic mechanisms of prednisone in ITP are not completely clear. The suggestion is that prednisone impairs the clearance of antibody-coated platelets, increases platelet production by interfering with the platelet destruction of the macrophages within the bone marrow, and stimulates megakaryocyte progenitors.[2,18]

There is a large variability in treatment regimens regarding the dose, the duration of full-dose treatment (two to six weeks) and the mode of tapering. About two-thirds of patients achieve a complete or partial response with prednisone 1 to 2 mg/kg, usually within seven to ten days.[19,20] Treatment is regarded to have failed when patients have not responded within three weeks.[19,20] Most patients relapse when the dose is reduced.[20,21] Around 20 to 40% have a durable remission.[7,13,14] Lower doses of corticosteroids (0.25 to 0.50 mg/kg/day) have been shown to have similar

efficacies to conventional doses (1 mg/kg/day) in adults.[22,23] Shorter courses of corticosteroid therapy have been investigated. Three studies examined the response rate of high-dose dexamethasone (30 to 40 mg/day in courses, four days a month) as first-line treatment.[24-26] The initial response was 80 to 89% with 42 to 59% of patients still in complete remission after a median follow-up of 31 months.[24,26] Initial treatment with high-dose dexamethasone might be safer and seems at least as effective as the conventional prednisone treatment as initial treatment. Despite these studies the optimal dose of therapy is unknown and some patients may be overtreated by aiming at complete remission.

Potential adverse effects of corticosteroids include signs and symptoms of hypercortisolism, diabetes, opportunistic infections and osteoporosis,[7] especially in patients who are ≥60 years, rendering long-term prednisone treatment less attractive.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) has been studied primarily in patients who were unresponsive to corticosteroids or who had contraindications to corticosteroids, such as uncontrolled diabetes mellitus. The mechanisms of action of IVIg are complex and not fully understood. Until recently, the effect was thought to be due to interference Fcγ-receptors (FcγR) mediated clearance of opsonised platelets,[27] but recent work has shown that IVIg slows the antibody-coated platelet destruction by increasing the expression of inhibitory FcRγRIIb on splenic macrophages.[28] Other mechanisms include the saturation of FcRn with IVIg, thereby increasing the clearance of autoantibodies.[27]

IVIg (0.4 g/kg/day for five days or 1.0 g/kg/day for two days) is effective in elevating the platelet count in approximately 75 to 92% of the patients.[7,29,30] Complete remission rates vary from 50 to 65%.[29] The responses are generally transient, lasting no more than three to four weeks, after which the platelet counts decrease to pretreatment levels.[7,14,29] The adverse effects of IVIg are generally mild. Approximately half of the patients have headaches, usually during the first infusion, sometimes combined with nausea and vomiting. In rare cases patients experience rigidity, drowsiness or lethargy, fever, photophobia, and painful eye movements.[29,30] Although IVIg is a plasma-derived product that can contain infectious agents, the nanofiltered formulation has proven to be efficacious, well tolerated, and safe.[31] The exact role of IVIg in adults with severe ITP is still controversial, mainly because of the transient effect and high costs. There is general agreement that IVIg should be administered in emergency situations and that it is a safe therapy in preparing patients for surgery.[11,29]

Anti D

Anti-D immunoglobulin is only effective in Rhesus D-positive non-splenectomised patients.[27] There are no extensive studies regarding the mechanism of action of anti-D. A direct interaction with macrophage FcγRs, thereby hampering destruction of platelets, is probably involved and is in agreement with the fact that anti-D is not effective after splenectomy.[27] Another effect might be the increased levels of inflammatory and other cytokines which can be observed immediately after anti-D infusion.[27]

In one study 70% of the adult patients responded to anti-D, and 33% had a complete or partial response.[32] The duration of response is highly variable from days up to several months.[32,33] There are questions regarding the dose: 50 μg/kg is usually sufficient, but 70 to 80 μg/kg could induce a faster response.[34,35] Repeated infusions can be used to maintain adequate platelet counts and such a strategy may enable patients to postpone or even avoid splenectomy.[32,34]

The adverse effects consist of flu-like symptoms such as headache, nausea, chills, fever, and dizziness. The expected extravascular haemolysis is usually mild, with clinically significant drops in haemoglobin levels being rare.[32,36]

Anti-D is an option for children with an acute ITP and elderly patients who are unfit to undergo splenectomy or have severe corticosteroid toxicity.[32] The delayed response of 48 to 72 hours after injection implies that this treatment can not be used in situations when an immediate rise in platelet count is necessary.[6,37]

Second-line treatment

Splenectomy

The first splenectomy for ITP was performed in 1916. Until the introduction of corticosteroids in the 1950s, splenectomy was considered the first-line therapy.[1]

After splenectomy 60 to 86% of patients have a partial or complete response and need no additional treatment.[10,12,38-41] More than 80% of platelet responses occur within several days after splenectomy, responses after ten days being unusual.[7,42] The relapse rate decreases as the interval from the time of splenectomy increases, and relapses after two years are rare.[38,41] Patients refractory after splenectomy should be evaluated for an accessory spleen, which is the case in 11%.[38]

Although the laparoscopic procedure has reduced surgical complications, splenectomy is not without risks. Apart from significant morbidity, perioperative mortality is 0.3 to 0.9%, and the long-term risk of sepsis and thrombosis has been described to be up to 6.3%.[12,38-40,43] Patients who are scheduled to undergo splenectomy should be immunised against streptococcal infections at least two weeks prior to splenectomy. Patients must be informed about the risk of infections with encapsulated micro-organisms and should have emergency antibiotics directly available.

Splenectomy is still regarded as the second-line therapy in refractory disease or corticosteroid dependency (>10 mg/day).[5,7,10,12,35]

Third-line and/or experimental treatment

Patients who do not respond to initial treatment or splenectomy are considered refractory (25 to 30% of the ITP patients).[19,29] These patients constitute a difficult management dilemma.[19] The chances of inducing a durable and sustained remission are low and options for treatment carry relatively high risks of adverse effects.[29]

Before starting the treatment the balance between bleeding risk and the risk of complications due to therapy should be carefully considered. Portielje *et al*. showed that death due to lethal infections, to which immune suppressive therapy probably contributed, exceeded death by bleeding.[10]

Evidence-based guidelines for treating refractory patients are not available, partly because very few patients have severe thrombocytopenia after splenectomy, the follow-up durations are short, the outcomes other than platelet counts are rarely described, and the case series are small and uncontrolled.[13]

Platelet clearance inhibitors

Danazol (200 mg 2-4 times daily), an attenuated androgen, is effective in 50 to 80% of patients,[39,44,45] sometimes inducing durable remissions. Responses occur slowly and therefore treatment should be continued for at least three to six months.[2,46] Older patients appear to respond best.[14,39,44,45] The adverse effects are mostly reversible and include hepatotoxicity (30%), virilisation and amenorrhoea in women, rash and weight gain.[2,39,44]

Vinca alkaloids (vincristine and vinblastine) stimulate thrombocytopoiesis and suppress humoral and cellular immunity. Vinca alkaloids infused intravenously over six to eight hours have a higher sustained response rate.[47] Vincristine is often complicated by substantial neuropathy,[2,14,29] vinblastine with leukopenia. Slowly infused vinca alkaloids have less and mild adverse effects.[47] Vinca alkaloids are used infrequently because response rates are low (<10%), and responding patients return to pretreatment platelet levels within days to weeks after cessation of therapy.[7,12,14]

Immunosuppressive therapy

Cyclophosphamide reduces the number of T and B lymphocytes and suppresses their function. Pulsed therapy with 1.0 to 1.5 g/m^2 at four-week intervals results in a response rate of 85%, with durable responses in up to 50% of patients.[48] Adverse effects, neutropenia, infections and thrombosis, were seen in 22% of the treatment courses.[48] Long-term adverse effects such as secondary malignancies[14,49] and sterility were not seen, although follow-up was short. Due to the possible long-term adverse effects, cyclophosphamide should only be used in severe cases of ITP not responding to other treatment.[50]

Cyclosporine suppresses the T-cell function, inhibits antigen-induced activation of $CD4^+$ T lymphocytes and the production of interleukin 2 and other cytokines.[51,52] Responses are seen in 50 to 55% of the patients, of which 30 to 40% have a complete response.[51,53] The induced response can persist for several months and even years after treatment has been discontinued.[49,51]

The majority of the patients experienced adverse effects, most frequently hypertension, severe muscle pain, increased creatinine, and headache. Up to one third of patients on high doses (5-6 mg/kg/day) discontinued treatment due to the adverse effects.[51] Lower doses (5 mg/kg/day for six days than reduced to 2.5 to 3 mg/kg/day) are generally well tolerated.[53]

Although large studies have not been performed and the toxicity profile is suboptimal, low-dose cyclosporine seems an effective alternative in refractory ITP patients.

Autologous peripheral blood stem cell transplantation (PBSCT) leads to a sustained response in a significant minority of chronic refractory ITP patients. Stem cells can be harvested after high-dose cyclophosphamide[54,55] with G-CSF or with G-CSF alone.[56] Passweg reported a remission in 50% of the patients and a sustained remission in 33%, lasting from seven to more than 48 months.[55,56] The treatment-related mortality is high 17%.[55] Because PBSCT is associated with a high toxicity rate, it might only be an option for patients who have a severe bleeding risk and who have not responded to any other treatment.

Experimental treatment

Experimental treatments are enthusiastically approached by clinicians because of the limitations of conventional therapy options. Most of the experimental agents have been described in case reports and case series.

Dapsone (75-100 mg/day orally) increases platelet counts by an as yet unknown mechanism. Competitive inhibition of the reticuloendothelial system could be one mechanism: dapsone induces haemolysis, phagocytosis of red blood cells might replace the destruction of antibody-coated platelets.[57] Dapsone has been shown to produce a partial or complete response in 40 to 50% of patients.[57-60] It seems less effective in patients with severe ITP. Adverse effects include cyanosis and methaemoglobinaemia, haemolysis, rash, nausea, vomiting, and headache.[57-60] The decrease in the haemoglobin level due to haemolysis is not correlated with the platelet count increase.[59] Treatment with dapsone can reduce the need for steroids in some patients.[60] Dapsone is well-tolerated and inexpensive, but most of the patients relapse when treatment is withdrawn. Removal of the spleen is superior to dapsone, but for patients unfit to undergo splenectomy it could be of value.

Helicobacter pylori (H. pylori) eradication therapy as treatment of ITP has primarily been described in Japanese and Italian studies.[61-65] Their clinical observations suggest that *H. pylori* could be involved in the pathogenesis of chronic ITP. The mechanisms responsible for the trigger of antiplatelet autoantibody production are unknown. *H. pylori* infection is seen in 43 to 75% of the ITP patients, the prevalence depending on the prevalence of *H. pylori* in the healthy population of the country in question.[61,63,64] The eradication treatment is effective in 84 to 100% of the infected chronic ITP patients.[61,63] Of the *H. pylori*-eradicated ITP patients 25 to 46% had a complete remission and 8 to 44% had a partial remission.[61,64,65] Predictive factors for response are high initial platelet count, short duration of illness and treatment in Italy or Japan. Although the evidence and follow-up are limited, treatment is simple, inexpensive, has limited toxicity and the advantage of avoiding long-term immunosuppressive treatment for those who respond. For severe ITP, with platelet levels <30, eradication therapy seems to be less effective. Investigation and eradication of *H. pylori* infection in chronic ITP patients with platelets count >30 might therefore be worthwhile.

Combination chemotherapy (cyclophosphamide, vincristine, prednisone, and procarbazine (CHOPP), cyclophosphamide, vincristine, etoposide (CEP), cyclophosphamide, vincristine, and prednisone (CVP)) was reported in 1993 by Figueroa *et al*. Six out of ten chronic refractory ITP patients, previously treated with at least steroids and splenectomy, had a complete response, four of which were durable after combination chemotherapy.[66] Another two patients had a partial response with one durable response and two of the ten patients died of intracerebral haemorrhage. The number of treated patients is small. The risk of inducing secondary malignancies and other toxicity should be carefully considered. Combination chemotherapy can prove to be a two-edged sword in treating patients who suffer from ITP in the context of a lymphoreticular malignancy.

Mycophenolate mofetil (MMF) is an immunsuppressive drug which is licensed for the prevention of acute rejection of allergenic organ transplants and haemopoietic stem cell transplantation. Additionally, it is used as second-line treatment in several autoimmune diseases.[67] Studies showed that MMF (1.5 to 2 g/d orally) results in response rates of 55 to 80% with 24 to 33% complete responses, lasting from two to more than 13 months.[67,68] The adverse effects were mild and reversible (nausea, diarrhoea, headache, and backache).[68] MMF merits further investigation to fully assess its efficacy and safety as a second-line treatment in refractory ITP patients.

Anti-CD20 monoclonal antibody (Rituximab) was originally used in patients with relapsed, low-grade B-cell non-Hodgkin's lymphoma and has obtained a central role in the treatment of B-cell malignancies. It binds specifically to CD20 antigen present on B-cells. *In vitro* studies have demonstrated induction of complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and apoptosis of the B cell. In ITP, B-cell depletion results in decreased autoantibody production.[69] After one infusion of rituximab, B-cells remain undetectable for four to nine months.[70] When used in ITP patients, rituximab has a response rate of 25 to 75%, with 25 to 50% being partial or complete remissions.[70-73] Remissions seem to be longer in patients who achieve a complete response and have been reported to last for up to three years.[72,73] Most patients respond quickly, within one to three weeks, but a minority of patients have a delayed response, nine to eleven weeks after treatment is started.[71,73,74] The mechanisms of action of the two types of response are unclear. The fast response may partly be due to a mechanism of Fc-receptor saturation by opsonised CD20-positive cells.[71,73] The delayed and maintained response is probably due to the B-cell depletion and its potential interference with the autoantibody production.[71,73] The great advantage is the lack of toxicity. Most studies describe minor toxicity such as grade 1 to 2 infusion reactions but delayed onset of neutropenia has also been described.[70,71,73-77] Recently, reactivation of hepatitis B virus (HBV) during rituximab therapy for chronic lymphocytic leukaemia was reported.[78] Rituximab seems to be a very promising treatment option for refractory ITP patients and is nowadays considered and investigated as a possible second-line therapy before splenectomy. The HOVON is investigating the possible place of rituximab in the treatment of chronic ITP in the Netherlands.

THERAPEUTIC STRATEGIES IN THE NETHERLANDS

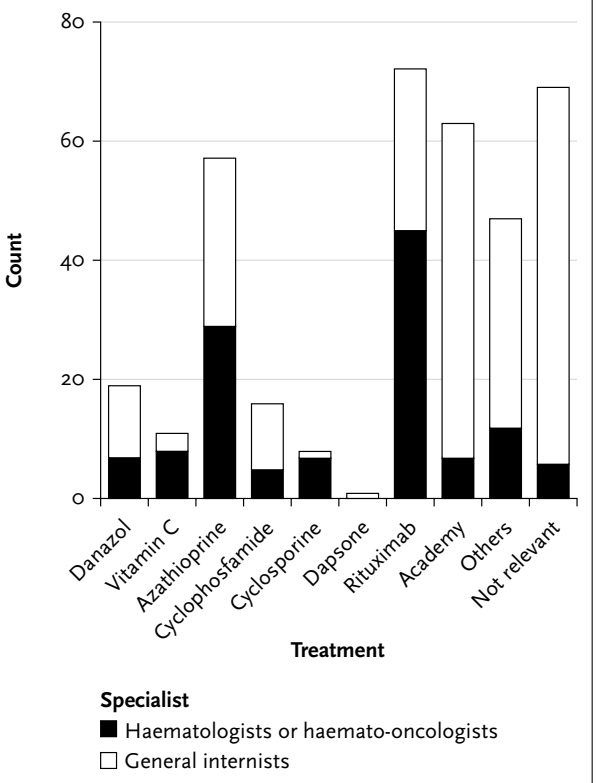
To examine which strategies are currently being used for the treatment of ITP, we contacted all registered internists in the Netherlands. In January 2005 we sent a simple and short questionnaire to all Dutch internists. Questions involved treatment indications, first- and second-line therapy preferences, as well as therapy preferences for refractory ITP. The collected data were analysed using SPSS-12.01.

The questionnaire was sent to 1542 Dutch internal medicine physicians, 388 (25%) of whom responded. Of the 388 respondents, 25 (6%) were no longer in practice, 105 (27%) were haematologists or haemato-oncologists, and 258 (66%) were general internists. Of the returned inquiries 363/388 (94%) were analysed.

Platelet counts <30 x 10^9/l are regarded as a treatment indication by 70% of the haematologists or haemato-oncologists and 52% of general internists. The other 30% of the haematologists or haemato-oncologists start treatment when platelet count is <50 x 10^9/l, or if there is

diathesis, or a combination of diathesis with low platelet count (*table 2*). Almost one third of the general internists refer ITP patients to a haematologist for treatment.
A majority of internists prescribe prednisolone 1 mg/kg/day for three weeks as the first-line therapy (232/363, 64%). The remaining internists use other steroid regimes such as dexamethasone 40 mg/day for four days or methylprednisone 500 mg for three days (*table 3*).
Splenectomy is regarded to be second-line therapy by 44%, while 105/363 (29%) use steroids for refractory or relapse ITP, and 27% use an other treatment (*table 4*).
Rituximab (72/363 (20%)) is the mostly commonly used treatment for refractory ITP patients after they have had a splenectomy and 57/363 (16%) use azathioprine. All the other treatments are used less frequently (*figure 1*). General internists referred 58/258 (22%) of the refractory ITP patients to a university hospital.

Figure 1. *Treatment options for chronic refractory ITP patients used by a number of haemotologists and haemato-oncologists versus general internists*



CONCLUSIONS

Although specific autoantibody tests are available, ITP remains a diagnosis of exclusion. The risk of severe bleeding is low, treatment is generally not indicated until platelet levels drop below 30 x 10^9/l. First-line treatment options remain corticosteroids and splenectomy.
Although a randomised comparison with other first-line treatments has not been performed, short courses of high-dose dexamethasone seem to be at least as effective and might avoid long-term maintenance therapy with low-dose corticosteroids.

Table 2. *Treatment indication according to speciality*

Specialist	Indication for treatment					
	Platelet count					
	<10	<20	<30	<50	Diathesis	Others
Haematologist or haemato-oncologist	4	29	40	10	5	17
General internists	25	67	43	29	20	74
Total	*29*	*96*	*83*	*39*	*25*	*91*

Table 3. *First-line treatment*

Specialist	Prednisone 20 mg	Prednisone 1 mg/kg per day for 3 weeks	Dexamethasone 40 mg per day for 4 days	Methylprednisone 500 mg for 3 days	Others
Haematologist or haemato-oncologist	2	77	8	13	5
General internists	12	155	10	17	64
Total	*14*	*232*	*18*	*30*	*69*

Table 4. *Treatment of refractory or relapses of idiopathic thrombocytopenic purpura*

Specialist	Steroids again	Splenectomy	Others
Haematologist or haemato-oncologist	25	73	7
General internists	80	87	91
Total	*105*	*160*	*98*

Splenectomy is still the most effective option for patients who are refractory or have a relapse after corticosteroids, but other treatments are emerging. Most third-line options are more or less experimental, with many adverse effects and limited or poorly studied therapeutic value. Low-dose cyclosporine seems an effective alternative in refractory patients. *H. pylori* eradication has the advantage of possibly avoiding long-term immune suppression for those who achieve a remission. Rituximab has also proven to be effective with few adverse effects, although large trials are lacking. Azathioprine and rituximab are used most frequently in the Netherlands as third-line treatment. Given the low rate of adverse events, rituximab seems an attractive, albeit expensive, alternative for splenectomy. The HOVON has opened a prospective, randomised phase II trial, the HOVON 64, exploring the role of different doses of rituximab in the treatment of refractory ITP.

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