

Management of Adult Idiopathic Thrombocytopenic Purpura

Ibrahim N. Nakhoul, MD, Peter Kozuch, MD, Mala Varma, MD

Dr. Nakhoul is a Fellow, Dr. Kozuch is an Assistant Professor of Clinical Medicine, and Dr. Varma is an Attending Physician in the Division of Hematology-Oncology at St. Luke's-Roosevelt Hospital Center, of the Continuum Cancer Centers of New York.

Address correspondence to:
Mala Varma, MD, St. Luke's-Roosevelt Hospital Center, Continuum Cancer Centers of New York, 1000 10th Avenue, Suite 11C02, New York, NY 10019;
Tel: (212) 523-7281; Fax: (212) 523-2004;
E-mail: mvarma@chpnet.org.

Abstract: Idiopathic thrombocytopenic purpura (ITP) is defined as isolated thrombocytopenia without a clinically apparent cause. It is categorized as acute, chronic, and refractory. Its clinical presentation ranges from acute to insidious and the bleeding may vary from minimal to severe. The target platelet count with therapy is more than 30,000/ μ L in sedentary individuals. Since studies regarding therapies for ITP have been mostly uncontrolled case series, the treatment recommendations are largely derived from expert opinion. This review paper summarizes the data on available therapies for adult acute and chronic/refractory ITP. The therapies include splenectomy, steroids, intravenous immunoglobulin, anti-Rh(D), monoclonal antibodies, danazol, chemotherapy, plasma exchange, and others.

Idiopathic thrombocytopenic purpura (ITP) is defined as isolated thrombocytopenia without a clinically apparent cause. Paul Gottlieb Werlhof first described it in 1735, and it was originally called Werlhof's disease. ITP is divided into two types: acute, lasting for less than 6 months, and chronic, persisting for more than 6 months. Refractory ITP is a term attributed to persistent thrombocytopenia despite adequate steroid treatment and splenectomy.

The pathogenesis of ITP is unclear but it is postulated that antibody-coated platelets undergo reticuloendothelial phagocytosis resulting in reduced platelet survival. However, not all patients have these auto-antibodies.¹ T cell-mediated cytotoxicity, antibody-mediated complement activation causing platelet lysis, and antibody-mediated suppression of megakaryocyte production have been suggested as other possible mechanisms.²

The incidence of ITP is 1.6/10,000 per year. Whereas some report that the disease is more common in women, others report no difference in gender distribution.³

The diagnostic hallmark of ITP is a low platelet count without identification of alternative causes of thrombocytopenia by history, physical, and laboratory evaluations. Tests should include peripheral blood smear examination, HIV testing in at-risk patients, and bone marrow biopsy to rule out myelodysplastic syndrome in patients above the age of 60.⁴ Assays for antiplatelet antibodies are not used

Keywords

ITP, idiopathic thrombocytopenic purpura, steroid, splenectomy, monoclonal antibodies, chemotherapy.

routinely.⁴ Platelet-associated immunoglobulin G (IgG) testing, though sensitive, lacks specificity. Assays for platelet antigen-specific antibodies are less sensitive but more specific; they may be helpful in distinguishing immune from nonimmune thrombocytopenias.⁵

Clinicians should be cognizant of other important possible diagnoses associated with thrombocytopenia including thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, disseminated intravascular coagulation, gestational thrombocytopenia, drug-induced thrombocytopenia, bacterial and viral infections (hepatitis, HIV), hypersplenism, myelodysplasia, acquired pure megakaryocytic aplasia, and congenital thrombocytopenias.

The clinical presentation in ITP ranges from acute to insidious and bleeding can vary from minimal to severe. In children, ITP usually has a self-limiting course resolving within 2–8 weeks in 80% of cases.^{4,6} The majority of adults develop chronic ITP.⁴ Bleeding in ITP is mucocutaneous and manifests as petechiae, purpura, easy bruising, epistaxis, gingival bleeding, and menorrhagia. The destruction of platelets by antibodies leads to an increase in the production of young platelets that are more effective in controlling hemostasis.⁷ Thus, bleeding manifestations are milder in patients with ITP compared with those of patients with thrombocytopenia of other etiologies. Serious bleeding rarely occurs if the platelet count is greater than 10,000/ μ L.⁸ About 40% of patients with platelet counts less than 10,000/ μ L develop major bleeds, including gastrointestinal bleeds, hematuria, and intracranial bleeding. The rate of fatal hemorrhage in untreated ITP is estimated to be 5%.⁴

Initial therapies for ITP are used to avert the risk of bleeding by promptly increasing the platelet count and to buy time for spontaneous remissions to occur. The target platelet count with therapy is more than 30,000/ μ L in sedentary individuals and more than 50,000–80,000/ μ L in patients with physically active occupations/lifestyles.⁹

Studies regarding therapies for ITP have been mostly uncontrolled case series. Treatment recommendations are therefore largely derived from expert opinion.⁴ The management of ITP should be approached according to the type of ITP and is summarized in Figure 1. When compared with acute ITP, the management of chronic/refractory ITP is challenging, but it is becoming more exciting with the emergence of new therapies.

This review summarizes the data on available therapies for adult acute and chronic ITP. A review of the Medline database from 1958 through March 2005 was performed. Keywords used were idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura, and ITP. While response criteria have not been historically uniform, platelet counts greater than 150,000/ μ L

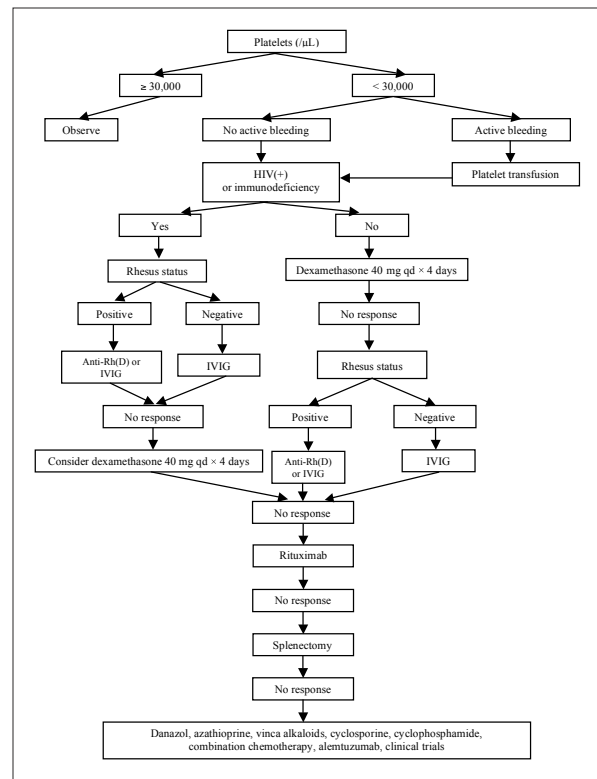


Figure 1. Suggested algorithm for the management of ITP.

IITP = idiopathic thrombocytopenic purpura; IVIG = intravenous immunoglobulin.

and platelet counts of 50,000–150,000/ μ L have typically defined complete response (CR) and partial response (PR), respectively. In most studies, sustained response was defined as a response lasting for more than 6 months.

Management of Acute ITP

Splenectomy

The first report of a successful therapy for ITP was in 1916, when Paul Kaznelson described a response to splenectomy. Splenectomy became first-line therapy for the next 35 years (Table 1). A recent review of a six-decade experience of splenectomy as secondary treatment for ITP by Kojouri and colleagues¹⁰ reported a CR rate of 66%. Relapses occurred in a median of 15% (range 0–51%) of patients with a median follow-up of 33 months (range 3–153 months). The time to relapse following splenectomy ranged from less than 1 month to more than 10 years.¹¹ The complication rate was 21.9% with laparotomy and 9.6% with laparoscopy.¹⁰ The mortality rate was 1% with laparotomy and 0.2% with laparoscopy.¹⁰ The death rate due to ITP or therapy complications in splenectomy-refractory patients was 15.7%.¹¹ Since the

Table 1. Management of Acute Idiopathic Thrombocytopenic Purpura

Therapy	Number of Patients, range	Response Rate, %	Duration of Response, mo
Splenectomy ^{10,11}	15–399	28–100	1–153
Regular dose Steroids ^{*12,13,15-18}	40–818	14–65	1–216
High dose steroids ^{†22-25}	10–125	44–100	0.25–60
IVIg ²⁶⁻³⁰	5–56	65–85	.75–1
Anti-Rh(D) ³¹⁻³⁵	10–272	70	.74–1.5

* Prednisone 15–120 mg or 0.3–3 mg/kg, prednisolone, methylprednisone, cortisone, or adrenocorticotropic hormone.

† Dexamethasone 40 mg per day for 4 days (single or multiple courses).

IVIg = intravenous immunoglobulin.

introduction of steroids for the treatment of ITP in the 1950s, splenectomy is no longer considered first-line therapy. While splenectomy may still be considered as second-line therapy if a 4–6 week course of steroids does not induce a sustained response, this operation is increasingly being deferred until other medical interventions, detailed below, have been attempted.

Steroids

Steroid therapy as treatment of ITP was first reported in 1958.¹² It is believed that steroids inhibit phagocytosis of antibody-coated platelets¹³ and inhibit autoantibody production.¹⁴ Steroids also appear to strengthen capillaries; bleeding manifestations often decrease before platelet counts rise.¹³

Steroid use in oral and intravenous formulations, in continuous and pulse schedules, and in “regular” and “high” dosages have been explored in both acute and chronic ITP. The most commonly used steroid regimen is prednisone at a dosage of 1 mg/kg per day orally for a duration of 2 weeks to 6 months. CR rates varied from 14% to 50% and PR rates from 2% to 40% when steroids were used as initial therapy.^{12,13,15-18} The rate of sustained CR following discontinuation of steroids varied from 14% to 32%. Continuation of steroids beyond 30–45 days did not confer additional benefit. Although short-term steroid use for ITP is well tolerated in general, reversible cushingoid features, gram-negative sepsis, and aspergillosis have been reported.^{19,20} Opportunistic infections have also been reported to complicate short-term steroid use in patients with AIDS.²¹ Therefore, in our practice, we usually avoid steroids in patients with AIDS-related ITP.

Oral and intravenous high-dose dexamethasone have been used in acute and chronic/refractory ITP, at a dosage of 40 mg/day for 4 days every 4 weeks. Cheng and associates²² treated 125 patients with newly diagnosed ITP with a single course of dexamethasone. Platelet

counts increased by at least 20,000/ μ L by the third day of treatment in 85% of patients. The overall response rate (ORR; CR+PR) was 85%; 50% had a sustained response for more than 6 months after a single course. Relapse rates were 43% and 50% at 3 and 6 months, respectively. Borst and coworkers²³ treated 18 patients with newly diagnosed ITP and another 18 patients with recurrent ITP with up to 6 cycles of oral dexamethasone. An acute response with an increase in platelet count to a level above 50,000/ μ L was seen in 83% of patients. When high-dose steroids were given as first-line treatment, the ORR was 89% and was sustained in 61% of patients at a median follow-up of 8.5 months. As second-line modality, ORR was also 89%, but was sustained in only 28% of patients at a median follow-up of 6 months. The efficacy of high-dose dexamethasone in chronic, refractory ITP has not been consistently demonstrated, although one study did show an overall response rate of 100% and a sustained CR rate of 100%.²⁴ High-dose dexamethasone is generally well tolerated with minor adverse effects comprised mainly of increased appetite and difficulty sleeping.²⁵ Because of its efficacy and favorable adverse-effect profile, high-dose dexamethasone is our preferred steroid regimen for initial therapy of ITP.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIg) at a dosage of 400 mg/kg per day for 5 days or 1 g/kg per day for 2 days has been used in the management of ITP. In 1983, Salama and colleagues²⁶ postulated that low titers of red cell alloantibodies contained in IVIg cause Fc receptor blocking. It was then demonstrated that following infusions of IVIg, clearance of autologous radiolabelled anti-Rh(D)-sensitized red cells is decreased, suggesting that IVIg works through Fc receptor blockade.^{27,28} The alloantibodies induce hemolysis and divert macrophages from antibody-bound platelet destruction.²⁶ IVIg can induce

an increase in platelet count to more than 50,000/ μ L in 70% of patients.^{10,26-30} The response is usually rapid; 7% and 79% of patients achieve platelet counts of more than 50,000/ μ L on the second and fifth day, respectively, following the start of IVIG therapy.³⁰ Thus, IVIG therapy is ideal when a rapid increase in platelet count is desired in patients with life-threatening bleeding.⁹ It can also be combined with steroids and platelet transfusions in these situations.⁹ Responses to IVIG usually last about 3 weeks and repeat cycles are frequently needed. However, the expense of this therapy and the length of infusion (8 hours daily for 2 days) limit its use in the chronic setting.

Anti-Rh(D)

Anti-Rh(D) is a plasma-derived immune globulin containing a high titer of antibodies to Rh(D) antigens. In contrast, IVIG has a distribution of IgG subclasses similar to that of normal plasma. Anti-Rh(D) binds to the Rh(D) antigen, and it is believed that the complex competitively inhibits reticuloendothelial phagocytosis of IgG-coated platelets.³¹ In 1984, Salama and colleagues³² reported on treatment of 10 Rh(D)-positive patients with chronic ITP with anti-Rh(D). Platelet counts increased in 8 out of 10 patients. Treatment response was poorer in the splenectomized (n=4) than in the nonsplenectomized (n=6), with mean platelet increments of 16,000/ μ L versus 60,000/ μ L, respectively. In a study of 27 Rh(D)-positive, HIV-negative, nonsplenectomized patients with acute ITP and platelet counts of less than 30,000/ μ L, a dose of 75 μ g/kg of intravenous anti-Rh(D) induced a median overnight increase in platelet count of 43,000/ μ L with a median duration of response of 46 days.³³ In HIV-related ITP, the effect of anti-Rh(D) was shown to last a mean of 11.6 days longer than that of IVIG (26.8 vs 15.2 days).³⁴

Cooper and coauthors³⁵ treated 28 patients with ITP refractory to steroids with intermittent anti-Rh(D). Anti-Rh(D) was infused whenever the platelet count was 30,000/ μ L or below. Twenty-six (93%) patients responded to the initial infusion of anti-Rh(D); 19 (68%) patients had repeated responses. At a median of 26 months, 12 (43%) of 28 patients had been off therapy for more than 6 months without undergoing splenectomy; 8 underwent splenectomy. The cost of anti-Rh(D) used in all 28 patients plus the cost of 8 splenectomies was less than the expected cost if splenectomies had been performed in all 28 patients. Thus, maintenance therapy with anti-Rh(D) may abrogate the need for splenectomy in more than 40% of patients.

Anti-Rh(D) is also less expensive than IVIG and requires a much shorter time period for infusion (5–10 minutes). The toxicity profile of anti-Rh(D), which includes mild hemolysis and infusional fever and chills, is more favorable than that of steroids. Although

considerably more expensive than steroid therapy, anti-Rh(D) should be considered for first-line therapy of ITP in the immunocompromised unsplenectomized Rh(D)-positive population. The efficacy of anti-Rh(D) therapy in splenectomized patients with accessory spleens has not been established.

Management of Chronic/Refractory ITP

Patients who have ITP persisting for more than 6 months (chronic ITP) or who have not responded to the treatments described above (refractory ITP) will ultimately need to be treated with the options outlined below and summarized in Table 2.

Monoclonal Antibodies

Rituximab Rituximab (Rituxan, Genentech) is a chimeric murine/human monoclonal antibody directed against the B-cell antigen CD20. It can induce profound B-cell depletion that may involve the autoreactive B-cell clone.³⁶ The regimen used in almost all studies is 375 mg/m² weekly for 4 consecutive weeks. There are two types of responses: early responses, occurring after the first or second infusion, and late responses, occurring at weeks 6–8.³⁷ It is postulated that a mechanism of macrophage blockade by opsonized B cells may account for the early responses.³⁶ The ORRs range from 23% to 100%.³⁶⁻⁴⁰ In the study by Cooper and coworkers,³⁸ 32% of patients had a sustained response at more than 1 year; half of those patients had not undergone prior splenectomy. The toxicity profile of rituximab is favorable; most adverse effects are limited to first infusion reactions. Due to its efficacy and favorable adverse effect profile, it may be preferable for patients with chronic/refractory ITP to try therapy with rituximab before undergoing splenectomy.

Alemtuzumab Alemtuzumab (Campath 1-H, Berlex) is a humanized anti-CD52 monoclonal antibody. CD52 is highly expressed on lymphocytes and monocytes. It is a 12-amino acid cell-surface glycoprotein that lies close to the cell membrane. Its function is not clear, but it may promote cell-cell adhesion or protect cells from insult.

Reports of alemtuzumab therapy for ITP are emerging. ORRs range from 44% to 80%.^{41,42} Lim and colleagues⁴² reported a response in 4 of 5 patients with refractory ITP treated with intravenous alemtuzumab. One response occurred after 3 days of therapy; the other responses occurred after 4–6 weeks. Responses lasted more than 4–9 months in 3 patients. It is believed that T-lymphocyte as well as B-lymphocyte depletion are mechanisms through which alemtuzumab is effective in ITP.⁴¹⁻⁴³

Adverse effects of intravenous alemtuzumab include

Table 2. Management of Chronic/Refractory Idiopathic Thrombocytopenic Purpura

Therapy		Number of Patients, range	Response Rate, %	Response Duration, mo
Monoclonal antibodies	Rituximab ³⁶⁻⁴⁰	3-57	23-100	1.75-41
	Alemtuzumab ^{41, 42}	5-9	44-80	2-17
Danazol ^{45-52,54}		7-96	0-67	1-182
Chemotherapy	Azathioprine ^{18,55-57}	6-53	50-100	1-132
	Vinca alkaloids ^{18,59-67}	6-42	17-90	0.25-24
	Cyclosporine ⁶⁸⁻⁷⁰	6-20	55-100	1-86
	Cyclophosphamide ^{18,66,71-73}	4-50	57-100	2-96
Combination chemotherapy ^{*74}		10	80	2-126
Plasma exchange ⁷⁵⁻⁷⁷		10-14	36-85	0.25-30
Interferon ⁷⁸⁻⁸⁰		9-21	0-85	1-8
Colchicine ⁸¹⁻⁸³		5-14	28-100	0.25-16
Dapsone ⁸⁴⁻⁸⁷		7-66	38-50	3-41
Vitamin C ⁸⁸⁻⁹⁰		11-14	0-82	1.75-30

* Chemotherapy regimens (repeated every 28 days):

- CVP: cyclophosphamide 400-650 mg/m² IV on days 1 and 8, prednisone 40 mg/m² orally on days 1-14, vincristine 2 mg IV on days 1 and 8.
- CMOPP: cyclophosphamide 400-650 mg/m² IV on days 1 and 8, prednisone 40 mg/m² orally on days 1-14, vincristine 2 mg on days 1 and 8, procarbazine 100 mg/m² orally on days 1-14.
- CEP: cyclophosphamide 400-650 mg/m² IV on days 1 and 8, prednisone 40 mg/m² orally on days 1-14, etoposide 100 mg/m² IV on days 14, 15, and 16.

fever, rigors, rash, nausea, hypotension, transient pancytopenia, prolonged lymphopenia, and opportunistic infections. Alemtuzumab is effective and has less hypotension, rash, and nausea when given subcutaneously.⁴⁴

Danazol

Danazol, a synthetic androgen, is believed to restore suppressor T-cell function and decrease antibody production,⁴⁵ decrease the number of available Fc receptors,⁴⁶ and decrease capillary wall permeability.⁴⁷ The conventional dose ranges from 200 to 800 mg orally daily.

The initial study published by Ahn and coworkers,⁴⁵ who treated 22 patients with danazol for at least 2 months, demonstrated an ORR of 59% with a median duration of response of 9 months. These results were not reproduced in subsequent smaller studies where the duration of therapy was only 2-3 months.⁴⁸⁻⁵⁰ Subsequently, two large studies by Ahn and colleagues⁵¹ and Maloisel and colleagues⁵² in which danazol was given for mean durations of 17.8 and 22.6 months, respectively, reported ORRs of 61.4%-67%. The median time to response was 3.1 months.^{51,52} Of note, 10-15% of patients responded after 6 or more months of therapy.^{51,52} Therefore a thera-

peutic trial of danazol should last at least 6 months.

Long-term remissions with danazol have been reported. Maloisel and colleagues⁵² reported a median duration of remission of 119 months and a sustained remission at 10 years in 42% of patients. Retreatment usually induces a response.^{51,52}

Some patients who do not respond to danazol 400-800 mg daily respond to 50 mg daily.⁵³ Notably, the time to response is longer with the lower dose.⁵¹⁻⁵³ Sustained responses have been reported in some nonsplenectomized patients, indicating that danazol may be an alternative to splenectomy.^{51,52,54} Danazol is well-tolerated. Adverse effects include weight gain or loss, lethargy, myalgias, liver dysfunction, skin rash, pruritus, and mild virilization. These adverse effects generally abate after several weeks of therapy or with a reduction in dose.

Chemotherapy

Azathioprine Azathioprine is given at a daily dose of 1-4 mg/kg (usually 150 mg) orally and modified according to the leukocyte count. Time to response varies from 2 to 10 months. Thus 6 months of treatment are needed

for assessment of its effectiveness. The reported CR and PR rates range from 17% to 71% and 5% to 83%, respectively.^{18,55-57} Therapy should be continued for 18 months in responders.⁵⁸ Response duration ranges from months to years. The major adverse effects are cytopenias, gastrointestinal symptoms, and secondary malignancy in younger patients.⁵⁸

Vinca Alkaloids The mechanism of action of vinca alkaloids could be related to inhibition of phagocytic cell function. Vincristine is given intravenously in 1–2 mg weekly doses for several weeks. Vinblastine is administered 0.1 mg/kg weekly for 5 weeks and repeated at biweekly then monthly intervals as maintenance therapy once a CR or PR is attained.⁵⁹ Although intravenous bolus and slow infusions (over 6 hours) of vinblastine yield equivalent responses,⁶⁰ slow infusional therapy of vincristine and vinblastine was associated with less hair loss and neutropenia than bolus injection therapy.⁶¹ Time to response is rapid (7–10 days). CRs and PRs range from 0 to 55% and 17% to 44%, respectively.^{18,59-67} Many of the reported responses are transient.^{59,62,64} The major adverse effects are peripheral neuropathy, alopecia, constipation, and extravasational injuries. If a sustained response is not achieved, vincristine therapy should be discontinued after 4–6 doses to avoid peripheral neuropathy.⁵⁸

Cyclosporine Cyclosporine A (CyA) is typically started at a daily dose of 5–6 mg/kg orally. Response rates vary from 30% to 75% and from 8% to 33% for CR and PR, respectively.⁶⁸⁻⁷⁰ In a study by Kappers-Klunne and colleagues,⁶⁸ 5 out of 10 unsplenectomized patients with chronic refractory ITP responded to CyA, but 9 ultimately required a splenectomy. Thus, CyA treatment may not obviate but rather may delay splenectomy in chronic ITP. Emilia and coworkers⁷⁰ treated 12 patients with refractory ITP with CyA for a median of 40 months. CR was achieved in 9 out of 12 (75%) patients and PR in 1 (8%) patient. A sustained response was seen in 60% of responders after discontinuation of CyA at a mean of 28.6 months after completion of therapy. Thus, CyA can be useful in a subgroup of patients with corticosteroid- and splenectomy-refractory ITP. However, treatment toxicity is significant, and it necessitated discontinuation of therapy in 30% of patients in one study.⁶⁸ Adverse effects consist of renal insufficiency, hepatotoxicity, hypertension, tremor, hirsutism, headache, muscle ache, gum hyperplasia, hypomagnesemia, and secondary cancer.

Cyclophosphamide Cyclophosphamide is given orally at dose of 1–2 mg/kg per day (usually 150 mg daily), or intravenously at a pulse dose of 1.0–1.5 g/m² every 3–4 weeks. Time to response is about 6–8 weeks.⁵⁸ CR

and PR range from 34% to 75% and 14% to 25%, respectively.^{18,66,71-73} Treatment should continue for 3 months beyond platelet count normalization.⁵⁸ Verlin and associates⁷¹ reported that remission rate appears to be related to duration of disease. Presence of disease for less than 1 year is associated with a response rate of 73% compared with disorders lasting over 2 years in which response rates were 40%. In a study by Reiner and colleagues,⁷² sustained CRs were seen in 8 out of 13 responders during follow-up intervals ranging from 7 months to 7 years (median 2.5 years) and sustained PRs were seen in 2 of 4 responders at 10-month and 4-year follow-up. Upon recurrence of ITP, 2 out of 5 patients responded to subsequent courses of cyclophosphamide. However, when relapse occurs, long-term risks such as secondary malignancy must be weighed against the benefits of resuming therapy. Adverse effects include cytopenias, hemorrhagic cystitis, gastrointestinal symptoms, sterility, and secondary cancers.

Huhn and colleagues⁷³ treated 14 adults with chronic refractory ITP with high-dose cyclophosphamide (50 mg/kg per day) followed by autologous lymphocyte-depleted peripheral blood stem cell transplantation. With up to 42 months follow-up, 6 patients had sustained CRs and 2 had sustained PRs; the ORR was 57%.

2-Chlorodeoxyadenosine Seven patients with refractory ITP were treated with 1–3 cycles of 2-chlorodeoxyadenosine administered by continuous infusion at a dosage of 0.1 mg/kg per day for 7 days. No improvement in platelet counts was observed.¹⁰⁰

Combination Chemotherapy

Figuroa and associates⁷⁴ published the results of combination chemotherapy in chronic refractory ITP (Table 2). Ten splenectomized patients were treated with up to 6 cycles of cyclophosphamide, prednisone, and one or more other agents (vincristine, procarbazine, and/or etoposide as in CVP, CEP, and CMOPP protocols). Six patients attained CRs and responses were sustained in 4 patients for over 11, 30, 54, and 126 months. Two patients attained a PR, which was sustained in 1 patient for over 9 months following completion of therapy. Discontinuation of therapy is recommended if no response is attained following 2 cycles of therapy. Responding patients may be given a total of 6 cycles at 4-week intervals.⁵⁸

Plasma Exchange

Intensive plasma exchange therapy with fresh-frozen plasma as replacement fluid has been used in the management of patients with acute and chronic ITP. The response rates range from 50% to 80% for CRs and 0 to 23% for PRs.⁷⁵⁻⁷⁷ Marder and colleagues⁷⁵ followed 14 patients with ITP for 1 year after plasma exchange therapy.

Exchange was performed prior to splenectomy in 8 of 9 patients with acute ITP and following splenectomy in 5 patients with chronic ITP. In the 9 patients with acute ITP, CR was attained in 5 patients (sustained for 80 weeks in 4 patients) and PR was seen in 1 patient. None of the patients with chronic ITP attained a response. Thus plasma exchange may be considered for the management of acute but not chronic ITP.

Interferon

Interferon alpha 2b has been used in refractory ITP, typically at a dosage of 3 million units subcutaneously 3 times a week for 4 weeks.⁷⁸⁻⁸⁰ Responses range from 0 to 100% and 0 to 60% for CR and PR, respectively.⁷⁸⁻⁸⁰ In a study by Vianelli and coworkers⁸⁰ none of 9 patients had any response. Retreatment with interferon after relapse may induce responses.^{78,79} Adverse effects include flu-like symptoms, fever, cytopenias, cardiomyopathy, hypotension, tachycardia, confusion, hepatotoxicity, depression, and respiratory depression.⁵⁸

Colchicine

The possible mechanism of action of colchicines in ITP is decreased clearance of opsonized platelets secondary to inhibition of microtubule-dependent events in macrophages.⁸¹ The recommended dosage is 0.5–0.6 mg 2 or 3 times daily orally for a minimum of 2 weeks. Response rates range from 14% to 67% and 7% to 71% for CR and PR, respectively.⁸¹⁻⁸³ Adverse events are usually mild.

Dapsone

Dapsone at a daily dose of 75–100 mg has demonstrated CR rates ranging from 0 to 25% and PR rates from 25% and 48%.⁸⁴⁻⁸⁷ The median duration of treatment required to obtain a response is 21 days. Godeau and colleagues⁸⁴ reported a sustained response in 19 out of 33 patients with a 12.5-month follow-up. However, thrombocytopenia recurs shortly after treatment withdrawal.⁸⁴ The most frequent adverse effect is dose-related hemolytic anemia at the 100-mg dose, which may abate at the lower dose of 50 mg.⁸⁵

Vitamin C

The first report of vitamin C in the treatment of refractory ITP was by Brox and colleagues in 1988.⁸⁸ The mechanism of action is not known. In subsequent studies the CR rate was very poor, in the 0–9% range. PR rates ranged from 0 to 82%.⁸⁸⁻⁹¹ Adverse effects of vitamin C include mainly dyspepsia.

Mycophenolate Mofetil

Twenty-one patients with refractory ITP were treated with mycophenolate mofetil (MMF) at a dosage of

1.5–2.0 g/day for a minimum of 12 weeks.⁹² The ORR was 62%. Five of 13 responders had a sustained response with the original dose of MMF for a median of 22 weeks. MMF was tapered or discontinued in the other 8 responders and 5 of these 8 responders relapsed as a result of dose reduction or withdrawal of MMF. Three patients showed sustained response after withdrawal of MMF, which was generally well tolerated with only slight nausea and diarrhea reported.⁹²

Protein A Immunoabsorption

It was postulated that protein A immunoabsorption decreases platelet activation and reduces platelet-binding immunoglobulin and circulating immune complex levels.⁹³ Snyder and coworkers⁹⁴ treated 72 splenectomized patients with chronic refractory ITP with staphylococcal protein A immunoabsorption. The regimen consisted of 6 treatments of 0.25–2.0 L plasma per procedure over 2–3 weeks. CR was attained in 25% and PR in 21% of patients. The median time to response was 2 weeks. Responses were sustained in 36% of patients over a follow-up period of up to 26 months. Hypersensitivity-type reactions were seen in 30% of cases. Low-dose steroids (<30 mg/d) can depress the incidence and severity of side effects.

Thrombopoietin and Thrombopoietin-like Agents

It was postulated that a mechanism leading to ITP is autoantibody-induced impairment of megakaryopoiesis and platelet production.⁹⁵ In a phase I/II clinical trial, pegylated recombinant human megakaryocyte growth and development factor (MGDF) induced a platelet response in 3 of 4 patients with refractory ITP.⁹⁶ Neutralizing antibodies and resultant thrombocytopenia have been reported in healthy volunteers and cancer patients undergoing chemotherapy treated with MGDF.⁹⁷ Therefore, development of MGDF has been halted. Bussel and colleagues⁹⁸ initiated a pilot study intended to enroll 12 patients with refractory ITP for treatment with oprelvekin (Neumega, Wyeth) 50 µg/kg per day subcutaneously for 21 consecutive days followed by 21 days of observation. The study was terminated after 7 patients were enrolled because of substantial toxicity and lack of efficacy. Also in development is AMG531 (Amgen), a thrombopoietic peptide. In a phase II study, 21 patients received a weekly dose of 1 µg/kg or 3 µg/kg for 6 weeks. Ten patients achieved a platelet count in the target range of 50,000–450,000/µL. Further development of this drug is in process.⁹⁹

WEB 2086 BS

Giers and associates¹⁰¹ treated 13 patients with chronic ITP for 14 days with 120 mg/day of the platelet-activating-factor antagonist WEB 2086 BS. Clinical bleeding

symptoms remained essentially unchanged in 9 patients and became more pronounced in the posttreatment period in 4 patients. In no case was an increase in platelet counts observed.

Conclusion

In summary, this article describes the therapeutic options for adult patients with ITP, as outlined in Figure 1. Selecting the right treatment depends on many factors that the treating physician should be aware of, and which are summarized below:

1. Type of ITP (acute vs chronic/refractory): Whereas the treatment of acute ITP is straightforward, the treatment of refractory ITP is more challenging given that the disease is more resistant and the list of available medications is long. Our preference is to start with monoclonal antibodies, especially rituximab, before moving to other available agents.
2. Time to Response: This is especially important when a quick rise in the platelet count is needed to prevent a major complication. The agents that produce the fastest increase in platelet count are IVIG, anti-Rh(D), and high-dose steroids. These are our drugs of choice for ITP patients who present with platelet counts less than 10,000/ μ L and/or signs or symptoms of bleeding.
3. Adverse Events: As an example, alemtuzumab seems to have good activity in the treatment of refractory ITP; however, its toxicity profile may hinder its use. Further studies are warranted to evaluate the best mode of administration for efficacy and for toxicity reduction.
4. Cost: Cost may hinder the use of active medications with minimal toxicities, such as rituximab, as first-line treatment.
5. Response Rate: Tables 1 and 2 summarize the response rates of the drugs used in the management of ITP.

Acknowledgment

This work is supported by the Hope Sheridan Foundation.

References

1. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med*. 2002;346:995-1008.
2. Olsson B, Andersson PO, Jernas M, et al. T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. *Nat Med*. 2003;9:1123-1124.
3. Michel M. "Why is it ITP?" presented at the sixth annual review of immune thrombocytopenic purpura, San Diego, Ca. December 3, 2004.
4. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood*. 1996;88:3-40.
5. Kuwana M, Okazaki Y, Kaburaki J, Ikeda Y. Detection of circulating B cells secreting platelet-specific autoantibody is useful in the diagnosis of autoimmune thrombocytopenia. *Am J Med*. 2003;114:322-325.
6. Kuhne T, Imbach P, Bolton-Maggs PH, Berchtold W, Blanchette V, Buchanan GR. Newly diagnosed idiopathic thrombocytopenic purpura in childhood: an observational study. *Lancet*. 2001;358:2122-2125.
7. Peng J, Friese P, Heilmann E, George JN, Burstein SA, Dale GL. Aged platelets have an impaired response to thrombin as quantitated by P-selectin expression. *Blood*. 1994;83:161-166.
8. Lacey JV, Penner JA. Management of idiopathic thrombocytopenic purpura in the adult. *Semin Thromb Hemost*. 1977;3:160-174.
9. Stasi R, Provan D. Management of immune thrombocytopenic purpura in adults. *Mayo Clin Proc*. 2004;79:504-522.
10. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. *Blood*. 2004;104:2623-2634.
11. McMillan R, Durette C. Long-term outcomes in adults with chronic ITP after splenectomy failure. *Blood*. 2004;104:956-960.
12. Watson-Williams EJ, Macpherson AI, Davidson S. The treatment of idiopathic thrombocytopenic purpura: a review of ninety-three cases. *Lancet*. 1958;2:221-226.
13. Jiji RM, Firozvi T, Spurling CL. Chronic idiopathic thrombocytopenic purpura: treatment with steroids and splenectomy. *Arch Intern Med*. 1973;132:380-383.
14. Shulman NR, Weinrach RS, Libre EP, Andrews HL. The role of the reticulo-endothelial system in the pathogenesis of idiopathic thrombocytopenic purpura. *Trans Assoc Am Physicians*. 1965;78:374-390.
15. Bunting WL, Kiely JM, Campbell DC. Idiopathic thrombocytopenic purpura: treatment in adults. *Arch Intern Med*. 1961;108:733-738.
16. Ikkala E, Kivilaakso E, Kotilainen M, Hastbacka J. Treatment of idiopathic thrombocytopenic purpura in adults: long-term results in a series of 41 patients. *Ann Clin Res*. 1978;10:83-86.
17. den Otlander GJ, Gratama JW, de Koning J, Brand A. Long-term follow-up study of 168 patients with immune thrombocytopenia: implications for therapy. *Scand J Haematol*. 1984;32:101-110.
18. Pizzuto J, Ambriz R. Therapeutic experience on 934 adults with idiopathic thrombocytopenic purpura: Multicentric Trial of the Cooperative Latin American group on Hemostasis and Thrombosis. *Blood*. 1984;64:1179-1183.
19. Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. *Blood*. 2001;97:2549-2554.
20. Apostolidis J, Tsandekidi M, Kousiades D, et al. Short-course corticosteroid-induced pulmonary and apparent cerebral aspergillosis in a patient with idiopathic thrombocytopenic purpura. *Blood*. 2001;98:2875-2877.
21. Singh N, Yu VL, Rihs JD. Invasive aspergillosis in AIDS. *South Med J*. 1991;84:822-827.
22. Cheng Y, Wong RS, Soo YO, et al. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. *N Engl J Med*. 2003;349:831-836.
23. Borst F, Keuning JJ, van Hulsteijn H, Sinnige H, Vreugdenhil G. High-dose dexamethasone as a first- and second-line treatment of idiopathic thrombocytopenic purpura in adults. *Ann Hematol*. 2004;83:764-768.
24. Andersen JC. Response of resistant idiopathic thrombocytopenic purpura to pulsed high-dose dexamethasone therapy. *N Engl J Med*. 1994;330:1560-1564.
25. Arruda VR, Annichino-Bizzacchi JM. High-dose dexamethasone therapy in chronic idiopathic thrombocytopenic purpura. *Ann Hematol*. 1996;73:175-177.
26. Salama A, Mueller-Eckhardt C, Kiefel V. Effect of intravenous immunoglobulin in immune thrombocytopenia. *Lancet*. 1983;2:193-195.
27. Bussel JB, Kimberly RP, Inman RD, et al. Intravenous gammaglobulin treatment of chronic idiopathic thrombocytopenic purpura. *Blood*. 1983;62:480-486.
28. Godeau B, Caulier MT, Decuyper L, Rose C, Schaeffer A, Bierling P. Intravenous immunoglobulin for adults with autoimmune thrombocytopenic purpura: results of a randomized trial comparing 0.5 and 1 g/kg b.w. *Br J Haematol*. 1999;107:716-719.
29. Godeau B, Chevret S, Varet B, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *Lancet*. 2002;359:23-29.
30. Godeau B, Lesage S, Divine M, Wirquin V, Farcet JP, Bierling P. Treatment of

- adult chronic autoimmune thrombocytopenic purpura with repeated high-dose intravenous immunoglobulin. *Blood*. 1993;82:1415-1421.
31. Sandler SG. Intravenous Rh immune globulin for treating immune thrombocytopenic purpura. *Curr Opin Hematol*. 2001;8:417-420.
 32. Salama A, Kiefel V, Amberg R, Mueller-Eckhardt C. Treatment of autoimmune thrombocytopenic purpura with rhesus antibodies (anti-Rh0(D)). *Blut*. 1984;49:29-35.
 33. Newman GC, Novoa MV, Fodero EM, Lesser ML, Woloski BM, Bussel JB. A dose of 75 microg/kg/d of i.v. anti-D increases the platelet count more rapidly and for a longer period of time than 50 microg/kg/d in adults with immune thrombocytopenic purpura. *Br J Haematol*. 2001;112:1076-1078.
 34. Scaradavou A, Woo B, Woloski BM, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. *Blood*. 1997;89:2689-2700.
 35. Cooper N, Woloski BM, Fodero EM, et al. Does treatment with intermittent infusions of intravenous anti-D allow a proportion of adults with recently diagnosed immune thrombocytopenic purpura to avoid splenectomy? *Blood*. 2002;99:1922-1927.
 36. Stasi R, Pagano A, Stipa E, Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. *Blood*. 2001;98:952-957.
 37. Stasi R, Stipa E, Forte V, Meo P, Amadori S. Variable patterns of response to rituximab treatment in adults with chronic idiopathic thrombocytopenic purpura. *Blood*. 2002;99:3872-3873.
 38. Cooper N, Stasi R, Cunningham-Rundles S, et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. *Br J Haematol*. 2004;125:232-239.
 39. Saleh MN, Gutheil J, Moore M, et al. A pilot study of the anti-CD20 monoclonal antibody rituximab in patients with refractory immune thrombocytopenia. *Semin Oncol*. 2000;27(6 suppl 12):99-103.
 40. Aggarwal A, Catlett JP. Rituximab: an anti-CD20 antibody for the treatment of chronic refractory immune thrombocytopenic purpura. *South Med J*. 2002;95:1209-1212.
 41. Willis F, Marsh JC, Bevan DH, et al. The effect of treatment with Campath-1H in patients with autoimmune cytopenias. *Br J Haematol*. 2001;114:891-898.
 42. Lim SH, Hale G, Marcus RE, Waldmann H, Baglin TP. CAMPATH-1 monoclonal antibody therapy in severe refractory autoimmune thrombocytopenic purpura. *Br J Haematol*. 1993;84:542-544.
 43. Ammatuna E, Marino C, Mitra ME, Calvaruso G, Iannitto E. Successful treatment of steroid resistant autoimmune thrombocytopenia associated with chronic lymphocytic leukemia with alemtuzumab. *Eur J Haematol*. 2004;73:225-226.
 44. Lundin J, Kimby E, Bjorkholm M, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). *Blood*. 2002;100:768-773.
 45. Ahn YS, Harrington WJ, Simon SR, Mylvaganam R, Pall LM, So AG. Danazol for the treatment of idiopathic thrombocytopenic purpura. *N Engl J Med*. 1983;308:1396-1399.
 46. Manoharan A. Danazol therapy in patients with immune cytopenias. *Aust N Z J Med*. 1987;17:613-614.
 47. Ambriz R, Pizzuto J, Morales M, Chavez G, Guillen C, Aviles A. Therapeutic effect of danazol on metrorrhagia in patients with idiopathic thrombocytopenic purpura (ITP). *Nouv Rev Fr Hematol*. 1986;28:275-279.
 48. McVerry BA, Auger M, Bellingham AJ. The use of danazol in the management of chronic immune thrombocytopenic purpura. *Br J Haematol*. 1985;61:145-148.
 49. Almagro D. Danazol in idiopathic thrombocytopenic purpura. *Acta Haematol*. 1985;74:120.
 50. Mazzucconi MG, Francesconi M, Falcione E, et al. Danazol therapy in refractory chronic immune thrombocytopenic purpura. *Acta Haematol*. 1987;77:45-47.
 51. Ahn YS, Rocha R, Mylvaganam R, Garcia R, Duncan R, Harrington WJ. Long-term danazol therapy in autoimmune thrombocytopenia: unmaintained remission and age-dependent response in women. *Ann Intern Med*. 1989;111:723-729.
 52. Maloisel F, Andres E, Zimmer J, et al. Danazol therapy in patients with chronic idiopathic thrombocytopenic purpura: long-term results. *Am J Med*. 2004;116:590-594.
 53. Ahn YS, Mylvaganam R, Garcia RO, Kim CI, Palow D, Harrington WJ. Low-dose danazol therapy in idiopathic thrombocytopenic purpura. *Ann Intern Med*. 1987;107:177-181.
 54. Edelmann DZ, Knobel B, Virag I, Meytes D. Danazol in non-splenectomized patients with refractory idiopathic thrombocytopenic purpura. *Postgrad Med J*. 1990;66:827-830.
 55. Quiquandon I, Fenaux P, Caulier MT, Pagniez D, Huart JJ, Bauters F. Re-evaluation of the role of azathioprine in the treatment of adult chronic idiopathic thrombocytopenic purpura: a report on 53 cases. *Br J Haematol*. 1990;74:223-228.
 56. Bouroncle BA, Doan CA. Treatment of refractory idiopathic thrombocytopenic purpura. *JAMA*. 1969;207:2049-2052.
 57. Picozzi VJ, Roeske WR, Creger WP. Fate of therapy failures in adult idiopathic thrombocytopenic purpura. *Am J Med*. 1980;69:690-694.
 58. McMillan R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. *Ann Intern Med*. 1997;126:307-314.
 59. Simon M, Jouet JP, Fenaux P, Pollet JP, Walter MP, Bauters F. The treatment of adult idiopathic thrombocytopenic purpura: infusion of vinblastine in ITP. *Eur J Haematol*. 1987;39:193-196.
 60. Facon T, Caulier MT, Wattel E, Jouet JP, Bauters F, Fenaux P. A randomized trial comparing vinblastine in slow infusion and by bolus i.v. injection in idiopathic thrombocytopenic purpura: a report on 42 patients. *Br J Haematol*. 1994;86:678-680.
 61. Ahn YS, Harrington WJ, Mylvaganam R, Allen LM, Pall LM. Slow infusion of vinca alkaloids in the treatment of idiopathic thrombocytopenic purpura. *Ann Intern Med*. 1984;100:192-196.
 62. Ahn YS, Harrington WJ, Seelman RC, Eytel CS. Vincristine therapy of idiopathic and secondary thrombocytopenias. *N Engl J Med*. 1974;291:376-380.
 63. Ahn YS, Byrnes JJ, Harrington WJ, et al. The treatment of idiopathic thrombocytopenia with vinblastine-loaded platelets. *N Engl J Med*. 1978;298:1101-1107.
 64. Manoharan A. Slow infusion of vincristine in the treatment of idiopathic thrombocytopenic purpura. *Am J Hematol*. 1986;21:135-138.
 65. Burton IE, Roberts BE, Child JA, Montgomery DA, Raper CG. Responses to vincristine in refractory idiopathic thrombocytopenic purpura. *Br Med J*. 1976;2:918.
 66. Kumar S, Diehn FE, Gertz MA, Tefferi A. Splenectomy for immune thrombocytopenic purpura: long-term results and treatment of postsplenectomy relapses. *Ann Hematol*. 2002;81:312-319.
 67. Kelton JG, McDonald JW, Barr RM, et al. The reversible binding of vinblastine to platelets: implications for therapy. *Blood*. 1981;57:431-438.
 68. Kappers-Klunne MC, van't Veer MB. Cyclosporin A for the treatment of patients with chronic idiopathic thrombocytopenic purpura refractory to corticosteroids or splenectomy. *Br J Haematol*. 2001;114:121-125.
 69. Emilia G, Messori C, Longo G, Bertesi M. Long-term salvage treatment by cyclosporin in refractory autoimmune haematological disorders. *Br J Haematol*. 1996;93:341-344.
 70. Emilia G, Morselli M, Luppi M, et al. Long-term salvage therapy with cyclosporin A in refractory idiopathic thrombocytopenic purpura. *Blood*. 2002;99:1482-1485.
 71. Verlin M, Laros RK, Jr, Penner JA. Treatment of refractory thrombocytopenic purpura with cyclophosphamide. *Am J Hematol*. 1976;1:97-104.
 72. Reiner A, Gernsheimer T, Slichter SJ. Pulse cyclophosphamide therapy for refractory autoimmune thrombocytopenic purpura. *Blood*. 1995;85:351-358.
 73. Huhn RD, Fogarty PF, Nakamura R, et al. High-dose cyclophosphamide with autologous lymphocyte-depleted peripheral blood stem cell (PBSC) support for treatment of refractory chronic autoimmune thrombocytopenia. *Blood*. 2003;101:71-77.
 74. Figueroa M, Gehlsen J, Hammond D, et al. Combination chemotherapy in refractory immune thrombocytopenic purpura. *N Engl J Med*. 1993;328:1226-1229.
 75. Marder VJ, Nusbacher J, Anderson FW. One-year follow-up of plasma exchange therapy in 14 patients with idiopathic thrombocytopenic purpura. *Transfusion*. 1981;21:291-298.
 76. Buskard N, Rock G, Nair R. The Canadian experience using plasma exchange for immune thrombocytopenic purpura. Canadian Apheresis Group. *Transfus Sci*. 1998;19(3):295-300.
 77. Blanchette VS, Hogan VA, McCombie NE, et al. Intensive plasma exchange therapy in ten patients with idiopathic thrombocytopenic purpura. *Transfusion*. 1984;24:388-394.
 78. Dubbeld P, Hillen HF, Schouten HC. Interferon treatment of refractory idiopathic thrombocytopenic purpura (ITP). *Eur J Haematol*. 1994;52(4):233-235.
 79. Proctor SJ. alpha Interferon therapy in the treatment of idiopathic thrombocytopenic purpura. *Eur J Cancer*. 1991;27(suppl 4):S63-68.
 80. Vianelli N, Tazzari PL, Baravelli S, Ricci F, Valdre L, Tura S. Interferon-alpha 2b is not effective in the treatment of refractory immune thrombocytopenic purpura. *Haematologica*. 1998;83:761-763.

Continued on page 153.