Management of Adult Patients with Persistent Idiopathic Thrombocytopenic Purpura Following Splenectomy

A Systematic Review

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Background: **Treatment of chronic refractory idiopathic thrombocytopenic purpura is a dilemma because many patients have minimal symptoms, response to treatment is uncertain, and treatments may have serious adverse effects.**

Purpose: **To determine the effectiveness of treatments for adult patients with idiopathic thrombocytopenic purpura who have not responded to splenectomy.**

Data Sources: **English-language reports from 1966 through 2003 that were retrieved from MEDLINE and Reference Update and bibliographies of retrieved articles.**

Study Selection: **Articles reporting 5 or more total patients were reviewed to select eligible patients. Patients were eligible for inclusion if they were more than 16 years of age, had idiopathic thrombocytopenic purpura for more than 3 months, had a previous splenectomy, and had a platelet count less than 50×10^9 cells/L.**

Data Extraction: **Patients were assessed for platelet count response, bleeding complications, duration of follow-up, and death. Complete remission was defined as a normal platelet count with no treatment for more than 3 months and for the duration of follow-up.**

Data Synthesis: **90 articles with 656 patients treated with 22 therapies met selection criteria. Azathioprine, cyclophosphamide, and rituximab had the most reported complete responses, but they were reported in only 41 to 109 patients. Reported complete response rates ranged from 17% to 27%, but 36% to 42% of patients had no response with these 3 treatments. Most reports described only platelet count responses; bleeding outcomes were reported in only 63 patients (10%). Only 111 (17%) of the 656 eligible patients had pretreatment platelet counts of less than 10×10^9 cells/L. No treatment method was reported in more than 20 patients.**

Conclusions: **Evidence for the effectiveness of any treatment for patients with idiopathic thrombocytopenic purpura and persistent severe thrombocytopenia after splenectomy is minimal. Potentially effective treatments must be evaluated by randomized, controlled trials to determine both benefit and safety.**

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Adult patients with idiopathic (immune) thrombocytopenic purpura who have severe thrombocytopenia are initially treated with glucocorticoids (1–3). Splenectomy has been a standard treatment for more than 50 years for patients who do not respond to initial glucocorticoid treatment, providing durable, complete remissions in about two thirds of patients (1–3). However, there is no consensus on appropriate management for patients with persistent severe thrombocytopenia after splenectomy (1–4). Management of these patients remains a dilemma. Persistent severe thrombocytopenia implies a risk for serious bleeding, yet many patients have minimal symptoms and may do well with no treatment (1–4). Recommended treatments often have adverse effects that may be serious and unacceptable. Many different treatments have been described with frequent reports of success, but the experience of many physicians suggests that responses are uncommon (2).

To understand and interpret the evidence for the many different reported treatments, we systematically reviewed (5) all articles describing treatment of adult patients with idiopathic thrombocytopenic purpura who had persistent thrombocytopenia after splenectomy. This review assesses the efficacy of the different treatments for achieving a durable complete response. Treatments used to achieve temporary platelet count responses or to manage acute bleeding episodes were not assessed.

METHODS

Our research strategy was to obtain individual-level patient outcome data from case series. We first identified studies that met our inclusion criteria. We then used 5 inclusion criteria to select specific patients from tables that contained patient-level data. If patient-level data were not available in the article but all patients in the article met the 5 inclusion criteria, we used the group-level data. We grouped the findings according to the treatment and recorded the platelet count response as well as the outcomes of bleeding and death. Finally, we aggregated the data into group-level findings for each treatment.

Literature Search

We used Ovid software to search the MEDLINE database from 1 January 1966 to 30 September 2003. Case series published before 1966 were excluded because they often included patients treated before current supportive care measures were available. Key words searched were *idiopathic thrombocytopenic purpura*, *immune thrombocytopenic purpura*, *idiopathic thrombocytopenia*, and *immune thrombocytopenia*. The MeSH subheading search was *idiopathic thrombocytopenic purpura*. These terms were combined with the 40 identified treatment methods that are listed in the text and **Table 1** (using both generic and brand names when appropriate) and with the phrases *treatment outcomes* or *treatment*. The search was limited to En-

glish-language reports. For publications from 1989 to 2003, alternative literature search software (Reference Update, Thomson ISI, Philadelphia, Pennsylvania) was also used. The bibliographies of all retrieved articles were searched for additional relevant articles.

Criteria for Article Selection

We determined selection criteria a priori to limit articles to reports describing treatment of adults. Our goal was to assess the effectiveness of treatments to establish a durable complete response. Articles published in pediatric journals were not retrieved. Articles describing treatment with glucocorticoids (except for regimens of intermittent high-dose dexamethasone) were excluded because glucocorticoids were used principally as adjunctive treatment with other therapies. Articles describing treatment with intravenous immunoglobulin and anti-Rh(D) were excluded because these agents were typically used to achieve a temporary platelet count response rather than a durable response. However, articles describing treatment with anti-(Rh)D-opsonized D^+erythrocytes were included because the authors stated that the goal of treatment was to establish a durable complete response. Supportive treatments, such as those with platelet transfusions and antifibrinolytic agents, were excluded. Articles reporting fewer than 5 total patients were excluded to avoid reports of exceptional patients. Articles reporting 5 or more total patients were reviewed to determine whether they described any eligible patients.

Criteria for Patient Selection

We selected patients by using 5 a priori criteria to define chronic refractory idiopathic thrombocytopenic purpura:

1. The diagnosis was idiopathic thrombocytopenic purpura (1).

2. The patients were adults, since spontaneous remissions occur in many children with persistent thrombocytopenia (6). Adults were defined as patients older than 16 years of age; when we reviewed the data, 16 years of age was the predominant age distinction for children and adults described in the reviewed articles.

3. The patients had undergone a splenectomy, because splenectomy is effective in most patients (1–3) and the goal of this review was to address management options for patients who had not responded to splenectomy.

4. The duration of idiopathic thrombocytopenic purpura was more than 3 months, a criterion established to exclude most patients who have a spontaneous remission (1) or in whom another cause of thrombocytopenia becomes apparent (7, 8).

5. The platelet count was less than 50×10^9 cells/L, since patients with platelet counts greater than 50×10^9 cells/L are not at risk for spontaneous major bleeding (1–3, 8).

Articles describing only group data were included if it was clear that all reported patients met the eligibility criteria. Patients were excluded if they were also reported in another publication or if the data were insufficient to assess the eligibility or response criteria. For example, in some articles, children could not be distinguished from adults or the course of different treatments could not be determined.

Key Summary Points

This review analyzed all reports from 1966 through September 2003 on the treatment of adult patients with idiopathic thrombocytopenic purpura who had persistent thrombocytopenia after splenectomy.

Current evidence supporting effectiveness and safety of any therapy is minimal. In this patient group, there are no randomized, controlled trials comparing 1 treatment with another or comparing treatment with observation alone.

Most reports describe only platelet count responses; bleeding symptoms are rarely described.

Agents that may be most promising for further study are cyclophosphamide, azathioprine, and rituximab; they must be evaluated for effectiveness and safety in randomized, controlled trials with assessment of clinical outcomes and platelet count responses.

Article Assessment

Two of the authors independently reviewed each article to determine patient eligibility. Each article that reported at least 1 eligible patient was further reviewed by 2 of the authors using a standard form and a priori criteria for outcome assessments of the individual patients or of group data. Disagreements were resolved by consensus among all of the authors. The level of evidence for each article with at least 1 eligible patient was defined as a randomized, controlled clinical trial; a nonrandomized clinical trial with contemporary or historical controls; a prospective cohort study of consecutive patients; a prospective study with enrollment of selected patients; a retrospective analysis of consecutive patients; or a retrospective analysis of selected patients. In some articles, the method of the study was not clearly described and the level of evidence was determined by consensus among the authors. To assess outcomes in patients who have greater risk for bleeding and therefore greater need for treatment, eligible patients were further separated into 3 groups according to their baseline platelet count before the treatment of interest: less than 50×10^9 cells/L, less than 30×10^9 cells/L, and less than 10×10^9 cells/L. Patients with a platelet count less than 10×10^9 cells/L were therefore included in the analysis of all 3 groups; patients with a platelet count less than 30×10^9 cells/L were included in 2 of the groups. Many patients were described only as having platelet counts less than 50×10^9 cells/L; therefore, analysis of separate patient groups defined by platelet counts of 30 to 50×10^9 cells/L, 10 to 30×10^9 cells/L, and less than 10×10^9 cells/L was not possible. Articles describing treatment with vincristine and vinblastine administered by intravenous bo-

Table 1. **Treatments for Chronic Refractory Idiopathic Thrombocytopenic Purpura***

Treatment†	Total Articles‡	Total Patients§	Articles Reporting Eligible Patients	Eligible Patients
	←	*n*		→
Azathioprine	19	248	10	109
Vinca alkaloids	34	454	12	103
Danazol	30	682	11	90
Cyclophosphamide	16	175	5	83
High-dose dexamethasone	13	176	8	50
Rituximab	10	107	8	41
Interferon	15	169	8	40
Cyclosporine	3	40	3	21
Accessory splenectomy	17	102	6	20
Vitamin C	11	132	8	20
Dapsone	8	155	5	15
Anti-(Rh)D-opsonized D^+ erythrocytes	2	22	2	10
Cyclophosphamide/stem-cell support	1	14	1	9
Mycophenolate mofetil	1	21	1	7
Interleukin-11	1	7	1	7
2-Chlorodeoxyadenosine	1	7	1	7
Colchicine	4	46	3	6
Plasma exchange	6	116	2	6
Combination chemotherapy	3	23	1	5
WEB 2086 BS	2	26	1	3
Campath-1H	2	27	1	2
Protein A immunoadsorption	9	157	1	2

* The treatments presented are those that were described in articles with 5 or more total patients that reported the treatment of patients with chronic refractory idiopathic thrombocytopenic purpura, as defined by the eligibility criteria presented in this review.
† Treatments are listed in the order of the number of eligible patients treated with each therapy.
‡ The total number of articles is the number of articles reporting 5 or more patients with each treatment.
§ The total number of patients is the number of all patients in the articles.

lus or infusion or by vinca-loaded erythrocytes are reported together as vinca alkaloids. Articles describing intravenous and oral cyclophosphamide were also combined; the article describing high-dose cyclophosphamide with stem-cell support is described separately.

Assessment of Platelet Count Response

We defined responses as complete, partial, or none. For a complete response, a normal platelet count (150×10^9 cells/L or as defined in the original report) had to be achieved and maintained while the patient received no treatment for at least 3 months and for the duration of observation. For a partial response, a platelet count more than 50×10^9 cells/L, more than 30×10^9 cells/L, or more than 10×10^9 cells/L, according to the patient's group, for any duration, with or without additional treatment, had to be achieved. Patients who qualified for complete remission were excluded. Therefore, some patients with partial responses may have had only trivial platelet count increments for brief durations while continuing to receive treatment. For no response, the platelet count did not increase to more than 50×10^9 cells/L, more than 30×10^9 cells/L, or more than 10×10^9 cells/L, according to the patient's group. Concurrent therapy, the duration of treatment, and the total duration of observation were recorded.

Assessment of Bleeding and Death

Definitions of bleeding were established as we reviewed the data. Bleeding was defined as major if it resulted in death, was intracranial, was described as uncontrollable, or was treated with platelet transfusions. Purpura and petechiae were defined as trivial bleeding. All other bleeding, such as epistaxis, gastrointestinal bleeding, or excessive vaginal bleeding, was defined as minor. If death was reported, we noted whether it was attributed to bleeding.

Role of the Funding Source

The DAISY Foundation, which supported Mr. Perdue during the course of this research, did not influence the design, conduct, and reporting of the study or the decision to submit these data for publication.

RESULTS

The literature search identified 289 articles that described treatment of adults with 40 different therapies that were used to achieve a durable response (**Figure**); 94 articles reporting fewer than 5 total patients were excluded from further review. The remaining 195 articles were reviewed to search for eligible patients; 656 patients in 90 articles met our eligibility criteria for chronic refractory idiopathic thrombocytopenic purpura and were evaluable for response to treatment. Individual data were available for 468 patients; 188 patients were assessed by using group data.

Eighteen of the 40 treatment methods were reported only in articles with fewer than 5 total patients or were not reported in eligible patients. These therapies (actinomycin

C, anti-FcγRI antibody, anti-FcγRIII antibody, anti-immunoglobulin apheresis, biscoclaurine, bupleurum, combination chemotherapy with stem-cell support, doxorubicin [liposomal], etoposide-loaded platelets, *Helicobacter pylori* eradication, heparin, 6-mercaptopurine, methotrexate, omeprazole, ribavirin, thioguanine, thrombopoietin, and Traditional Chinese Medicine) were not evaluated. The 656 eligible patients were treated with 22 therapies. **Table 1** presents the number of articles (and the total number of patients in these articles) that reported 5 or more total patients and described treatment of at least 1 patient with 1 of these 22 therapies. **Table 1** also presents the number of articles that reported at least 1 eligible patient and the number of eligible patients treated with each therapy. Most articles did not describe eligible patients, and most patients in these articles did not meet our selection criteria.

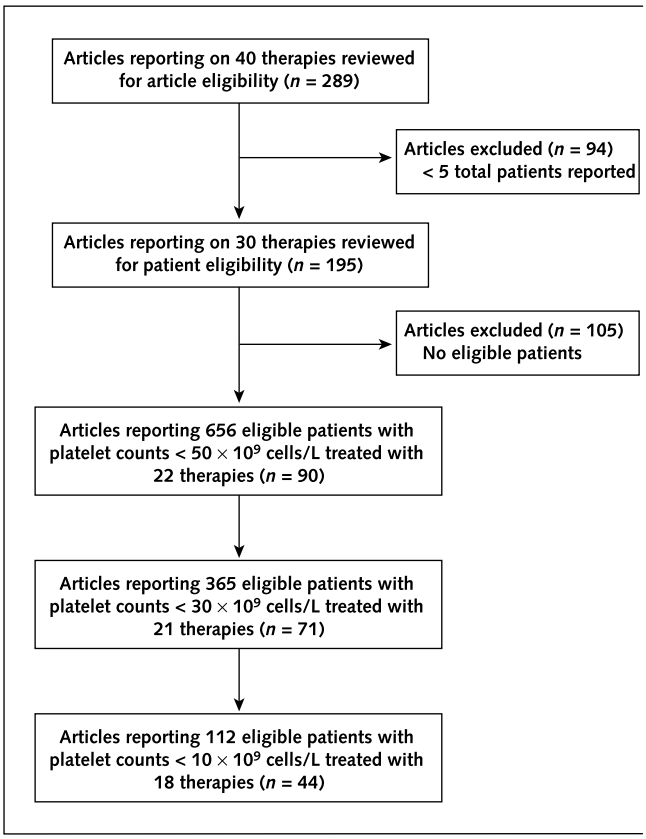
Appendix Table 1 (available at www.annals.org) presents data on each of the 90 articles that reported eligible patients treated with 22 therapies. A few articles and sites provided most of the eligible patients for some treatments. One study from several sites in South and Central America (9) that reported results of treatment with azathioprine, vinca alkaloids, and cyclophosphamide described 120 patients, 41% of all eligible patients treated with these 3 drugs. For azathioprine, 73% of the eligible patients are from only 2 articles, the South and Central American study (9) and a study from Lille, France (10). For vinca alkaloids, 40% of the eligible patients and 8 of the 9 patients with complete responses are from the University of Miami, Miami, Florida (11–13). For high-dose dexamethasone, all complete responses are from 1 of the 8 reports (14). For interferon, 53% of the patients are described in 1 report from Maastricht, the Netherlands (15), but all patients with complete responses are from another site, Newcastle, United Kingdom (16–18). Seven treatments each had only 1 published report with eligible patients.

Eighty-nine (99%) of the 90 articles reporting evaluable patients were cohort studies or case series without controls. However, the strength of evidence from these studies was variable. One hundred eighty-two (28%) of the eligible patients were reported from prospective cohort studies of consecutive patients; 279 (43%) of the eligible patients were apparently from retrospective analyses of selected patients. One report (19) was a randomized clinical trial; however, the randomization was not relevant for our analysis because only 8 of 42 patients had undergone splenectomy and the study compared 2 methods of vinblastine administration. There are no reported randomized clinical trials specifically studying patients with chronic idiopathic thrombocytopenic purpura who have not responded to splenectomy.

Appendix Table 1 (available at www.annals.org) also demonstrates that only 366 (56%) and 111 (17%) of the eligible patients were reported to have pretreatment platelet counts less than 30×10^9 cells/L and less than 10×10^9 cells/L, respectively. The 22 different treatments described for patients with platelet counts less than 50×10^9 cells/L were reported in 2 to 109 patients (median, 13 patients); the 17 treatments described for patients with platelet counts less than 10×10^9 cells/L were reported in only 1 to 20 patients (median, 3 patients). Part of the explanation for the identification of so few patients with platelet counts less than 30×10^9 cells/L and less than 10×10^9 cells/L is that the large South and Central American study (9) and other studies described patients only as having platelet counts less than 50×10^9 cells/L.

Table 2 describes the platelet count responses for each treatment according to the 3 groups of pretreatment platelet counts. Only 4 treatments (cyclophosphamide, azathioprine, rituximab, and high-dose dexamethasone) were reported in more than 10 patients who had platelet counts less than 10×10^9 cells/L and were also reported to cause complete remissions. For 8 treatments, no complete responses were reported. For all 656 patients analyzed in our

Figure. **Article and patient selection.**



Articles were retrieved for review if their journal, title, or abstract suggested that they contained evaluable data on eligible patients and indicated that they did not primarily report on children. Retrieved articles were not reviewed if they were reviews or other articles with no patient data; if they did not report on a treatment of interest, defined in the Methods section as treatment with the goal of a durable remission; or if they reported fewer than 5 total patients. Reviewed articles were excluded if they did not contain eligible patients. The primary platelet count criterion for eligibility was less than 50×10^9 cells/L; patients were further separated into groups with platelet counts less than 30×10^9 cells/L and less than 10×10^9 cells/L.

Table 2. **Response to Treatment of Patients with Chronic Refractory Idiopathic Thrombocytopenic Purpura**

Treatment*	Pretreatment Platelet Count	Patients	Response to Treatment		
			Complete	Partial	None
	$\times 10^9$ cells/L	n	←	n (%)	→
Azathioprine	<50	109	18 (17)	51 (47)	40 (36)
	<30	53	10 (19)	35 (66)	8 (15)
	<10	16	4 (25)	12 (75)	0
Vinca alkaloids	<50	103	9 (9)	46 (45)	48 (46)
	<30	34	2 (6)	17 (50)	15 (44)
	<10	8	0	5 (63)	3 (37)
Danazol	<50	90	1 (1)	53 (59)	36 (41)
	<30	52	0	37 (71)	15 (29)
	<10	15	0	14 (93)	1 (7)
Cyclophosphamide	<50	83	22 (27)	29 (35)	32 (38)
	<30	28	11 (39)	8 (29)	9 (32)
	<10	20	8 (40)	7 (35)	5 (25)
High-dose dexamethasone	<50	50	5 (10)	15 (30)	30 (60)
	<30	46	5 (11)	20 (43)	21 (46)
	<10	11	3 (27)	7 (64)	1 (9)
Rituximab	<50	41	10 (24)	14 (34)	17 (42)
	<30	35	8 (23)	15 (43)	12 (34)
	<10	13	5 (39)	6 (46)	2 (15)
Interferon	<50	40	3 (8)	12 (30)	25 (63)
	<30	28	1 (4)	11 (39)	16 (57)
	<10	3	1 (33)	1 (33)	1 (33)
Cyclosporine	<50	21	6 (21)	10 (48)	5 (31)
	<30	8	3 (38)	4 (58)	1 (12)
	<10	1	0	1 (100)	0
Accessory splenectomy	<50	20	5 (25)	9 (45)	6 (30)
	<30	9	3 (33)	5 (56)	1 (11)
	<10	2	2 (100)		0
Vitamin C	<50	20	0	5 (25)	15 (75)
	<30	16	0	7 (44)	9 (56)
	<10	3	0	2 (67)	1 (33)
Dapsone	<50	15	1 (7)	6 (40)	8 (53)
	<30	12	0	6 (50)	6 (50)
	<10	4	0	1 (25)	3 (75)
Anti-(Rh)D-opsonized D^+ erythrocytes	<50	10	3 (30)	1 (10)	6 (60)
	<30	5	0	0	5 (100)
	<10	2	0	0	2 (100)
High-dose cyclophosphamide with stem-cell support	<50	9	3 (33)	2 (22)	4 (45)
	<30	9	3 (33)	2 (22)	4 (45)
	<10	5	2 (40)	2 (40)	1 (20)
Mycophenolate mofetil	<50	7	0	4 (57)	3 (43)
	<30	7	0	5 (71)	2 (29)
	<10	0	–	–	–
Interleukin-11	<50	7	0	0	7 (100)
	<30	7	0	0	7 (100)
	<10	5	0	5 (100)	0
2-Chlorodeoxyadenosine	<50	7	0	0	7 (100)
	<30	0	–	–	–
	<10	0	–	–	–
Colchicine	<50	6	2 (33)	4 (67)	0
	<30	5	2 (40)	3 (60)	0
	<10	1	0	1 (100)	0
Plasma exchange	<50	6	0	0	6 (100)
	<30	1	0	0	1 (100)
	<10	1	0	0	1 (100)
Combination chemotherapy	<50	5	2 (40)	2 (40)	1 (20)
	<30	4	1 (25)	2 (50)	1 (25)
	<10	0	–	–	–
WEB 2086 BS	<50	3	0	0	3 (100)
	<30	3	0	0	3 (100)
	<10	1	0	0	1 (100)
Campath-1H	<50	2	0	2 (100)	0
	<30	1	0	1 (100)	0
	<10	0	–	–	–
Protein A immunoadsorption	<50	2	0	0	2 (100)
	<30	2	0	0	2 (100)
	<10	1	0	0	1 (100)

* Treatments are listed in the order of the number of eligible patients treated with each therapy.

review, the overall complete response rate was 14%; 46% had no response. Responses for the 142 patients in more recent articles, published from 1998 to 2003, were similar: Fourteen percent had complete responses and 39% had no response, even though a higher percent of the more recent articles are prospective studies of consecutive patients.

Concomitant medicines were reported for 125 (27%) of the 468 eligible patients for whom individual data were available. The use of concomitant medicines could not be assessed for the 188 patients reported as group data. One hundred nine (87%) of the 125 patients received glucocorticoids; 27 of these 109 patients plus the other 16 patients received 1 or more additional treatments. Although concomitant treatment with glucocorticoids and other agents may have enhanced the response to the treatments reviewed here, their effect cannot be assessed from these data.

Fifteen deaths among the 656 eligible patients were reported in 10 of the 90 articles. Of the 15 deaths, 9 were attributed to hemorrhage. Of these, 3 were due to intracranial hemorrhage, 1 was due to gastrointestinal bleeding, and 5 were due to bleeding at an unspecified site. However, bleeding outcomes were described in only 63 (10%) of the 656 eligible patients. Absence of bleeding symptoms was described in 29 patients, major bleeding was reported in 14 patients, minor bleeding was reported in 5 patients, and trivial bleeding (purpura) was reported in 15 patients. Duration of follow-up was reported for 463 of the 468 eligible patients for whom individual data were available; the median follow-up was 26 weeks (range, 2 days to 14 years). Follow-up duration was reported in 4 of the 7 articles presenting group data; these 4 articles described the median follow-up in 35 patients as 2 to 64 months.

Discussion

The most difficult problem a physician encounters in the management of idiopathic thrombocytopenic purpura is the patient who has persistent severe thrombocytopenia, often defined as a platelet count less than 10×10^9 cells/L (4), after failure of initial treatment with glucocorticoids and splenectomy. The difficulty is magnified because idiopathic thrombocytopenic purpura often occurs in otherwise healthy young adults, because low platelet counts may persist for many years with minimal bleeding symptoms, and because recommended treatments may have substantial risk. Although many treatments have been recommended for these patients, there are no evidence-based recommendations for when different treatments should be used or even for when any treatment should be used rather than managing a patient by observation alone (1–4).

The principal reason for this management dilemma is the inability to balance the risk for severe bleeding against the risk for complications of treatment, because the prognosis of individual patients with chronic refractory idiopathic thrombocytopenic purpura is so variable. Some patients may require intensive treatment to prevent recurrent severe bleeding. Other patients with equally low platelet counts may remain relatively asymptomatic for many years; in these patients, the adverse effects of treatment often exceed the benefits. This dilemma is documented in a case series of 124 consecutive adult patients with severe idiopathic thrombocytopenic purpura followed for a median duration of 9.4 years. In that series, 2 patients (1.6%) died from bleeding (intracerebral hemorrhage) while 3 patients (2.4%) died from infection related to glucocorticoids; 1 patient was also receiving other immunosuppressive treatment (8).

Four additional reasons for this management dilemma are documented by our systematic review. First, in articles describing treatment of idiopathic thrombocytopenic purpura, very few patients have severe thrombocytopenia after splenectomy. The total published literature on adult patients who can be identified to have platelet counts less than 50×10^9 cells/L after splenectomy describes only 656 patients. Our selection criterion of a platelet count less than 50×10^9 cells/L included many patients who may have required no treatment, because patients with platelet counts greater than 30×10^9 cells/L have negligible risk for bleeding (8, 20). Even patients with more severe thrombocytopenia may be safely observed without treatment if they have no bleeding symptoms (4). The total published literature on adult patients with platelet counts less than 10×10^9 cells/L after splenectomy describes only 111 patients. Therefore, there is minimal basis to provide guidance for management of patients with persistent severe thrombocytopenia after splenectomy.

Second, no reported randomized clinical trials specifically studied patients with chronic idiopathic thrombocytopenic purpura who had not responded to splenectomy. Comparison of treatment with observation alone may be important to document the effectiveness of treatment, because spontaneous remissions of chronic refractory idiopathic thrombocytopenic purpura can occur (1, 8, 21). Although the rate of spontaneous remissions in adults may be low, the rates of responses reported for many treatments are also low (**Table 2**). Comparison of treatment with observation alone may also be important to document the risks associated with treatment, because some immunosuppressive agents may exacerbate thrombocytopenia and increase the risk for bleeding.

Third, for some treatments, most or all of the patients with complete responses are reported from 1 site, and these results have not been reproduced at other sites. Fourth, no reported treatments are successful for achieving a complete response in most patients, and more recent reports have not described better results.

The main limitation of this review is the difficulty evaluating case series and interpreting patient outcomes. In most articles, either the patients did not meet our criteria for chronic refractory idiopathic thrombocytopenic purpura or the criteria could not be evaluated. Some articles with many patients were excluded from our review because only group data were reported and potentially eligible pa-

tients could not be distinguished from patients with platelet counts greater than 50×10^9 cells/L or from patients who had not had a splenectomy. For some treatments, most data are from few reports. In many of the studies, the data were from retrospective analyses of selected patients. Most reports described only the platelet count response. Although prevention of bleeding is the goal of treatment for patients with idiopathic thrombocytopenic purpura, bleeding symptoms were rarely described. Nineteen percent of eligible patients received concomitant medicines in addition to their primary treatment. Although the effect of concomitant medicines could not be evaluated from the limited descriptions available, these patients were included in our analysis because the authors' descriptions focused on the primary treatment method and because the use of concomitant medicines was common.

Our systematic review demonstrates that current evidence supporting effectiveness and safety of any therapy in patients with severe chronic refractory idiopathic thrombocytopenic purpura is minimal. The numbers of patients reported for all treatments are few, follow-up durations are short, and outcomes other than platelet count responses are rarely described. Some treatments, such as those with vinca alkaloids and danazol, caused relatively few complete responses. For other treatments, either the frequency of complete responses was low or the number of patients reported was few. On the basis of the frequency of complete responses and the number of patients reported, the treatments that may be most promising for further study are cyclophosphamide, azathioprine, and rituximab. However, even with these agents, experience is limited in patients who most need treatment—those with platelet counts less than 10×10^9 cells/L after splenectomy. Before physicians can confidently know the best management for their patients, these treatments, and perhaps combinations of agents as well as new approaches to treatment, must be evaluated for effectiveness and safety in prospective cohort studies of consecutive patients and randomized, controlled trials with measurements of clinical outcomes and platelet count responses.

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Appendix Table 1. **Articles Reporting Treatment of Eligible Patients with Chronic Refractory Idiopathic Thrombocytopenic Purpura**

Treatment and Country (City)	Year	Reference	Site*	Study Type†	Total Patients	Treated Patients	Platelet Counts of Eligible Patients‡		
							<50 × 10^9 cells/L	<30 × 10^9 cells/L	<10 × 10^9 cells/L
				← n →			← n (%) →		
Azathioprine									
United States (multiple)	1966	22	2	1	46	14	2 (0)	1	0
United States (New York, NY)	1967	23	1	4	8	8	3 (0)	1	0
United States (Columbus, OH)	1969	24	1	4	17	17	12 (25)	10	4
Italy (Genoa)	1971	25	1	4	21	21	1 (0)	1	0
Germany (Marburg)	1973	26	1	4	5	3	3 (0)	3	1
India (Chandigarh)	1979	27	1	3	30	1	1 (0)	0	0
United States (Stanford, CA)	1980	21	1	3	38	6	5 (0)	5	2
South and Central America	1984	9	2	4	934	41	41 (20)	0	0
France (Lille)	1990	10	1	4	53	53	39 (18)	32	9
United States (Rochester, MN)	2002	28	1	3	140	2	2 (0)	0	0
Vinca alkaloids									
United States (Miami, FL)	1974	11	1	4	43	21	13 (8)	13	0
United Kingdom (Leeds, Hull)	1976	29	2	4	9	9	3 (0)	2	1
United States (Miami, FL)	1978	12	1	4	11	11	8 (0)	7	2
Canada (Hamilton, Ontario)	1981	30	1	2	6	6	2 (0)	1	1
Singapore	1982	31	1	4	12	12	2 (0)	2	0
United States (Miami, FL)	1984	13	1	4	24	24	20 (30)	0	0
South and Central America	1984	9	2	4	934	29	29 (0)	0	0
United Kingdom (Belfast, Northern Ireland)	1985	32	1	4	5	5	1 (0)	1	0
Australia (Sydney)	1986	33	1	2	10	10	1 (100)	1	0
France (Lille)	1987	34	1	4	16	16	9 (0)	7	4
France (Lille)	1994	19	1	1	42	42	8 (0)	0	0
United States (Rochester, MN)	2002	28	1	3	140	7	7 (0)	0	0
Danazol									
United States (Miami, FL)	1983	35	1	2	22	22	12 (0)	10	2
United Kingdom (Liverpool)	1985	36	1	2	10	10	6 (0)	0	0
Mexico (Mexico City)	1985	37	1	2	21	21	16 (0)	13	4
Italy (Bergamo)	1985	38	1	2	14	14	4 (0)	0	0
Mexico (Mexico City)	1986	39	1	2	25	25	20 (0)	16	5
United States (Miami, FL)	1987	40	1	2	24	24	1 (100)	0	0
Australia (Sydney)	1987	41	1	2	12	5	1 (0)	1	0
United States (Philadelphia, PA)	1987	42	1	4	6	5	1 (0)	1	1
France (Lille)	1990	43	1	2	22	22	12 (0)	10	3
Japan (Chiba)	1992	44	2	2	14	14	1 (0)	1	0
United States (Mayo, Rochester, MN)	2002	28	1	3	140	16	16 (0)	0	0
Cyclophosphamide									
United States (Ann Arbor, MI)	1976	45	1	1	30	30	17 (41)	16	12
United States (Stanford, CA)	1980	21	1	3	38	1	1 (0)	1	0
Central and South America	1984	9	2	4	934	50	50 (22)	0	0
United States (Seattle, WA)	1995	46	1	2	20	17	11 (36)	11	8
United States (Rochester, MN)	2002	28	1	3	140	4	4 (0)	0	0

Appendix Table 1—**Continued**

Treatment and Country (City)	Year	Reference	Site*	Study Type†	Total Patients	Treated Patients	Platelet Counts of Eligible Patients‡		
							<50 × 10^9 cells/L	<30 × 10^9 cells/L	<10 × 10^9 cells/L
				← n →			← n (%) →		
High-dose dexamethasone									
United States (Detroit, MI)	1994	14	1	1	10	10	6 (83)	6	4
France (Lille)	1995	47	1	2	10	10	9 (0)	9	1
France (multiple)	1996	48	2	2	7	7	4 (0)	4	1
Brazil (Campinas)	1996	49	1	2	18	18	5 (0)	3	1
Canada (Hamilton, Ontario)	1997	50	1	2	9	9	5 (0)	5	3
Turkey (Ankara)	1997	51	1	1	10	10	10 (0)	10	0
Italy (Albano Laziale)	2000	52	2	2	32	32	9 (0)	9	1
United States (Rochester, MN)	2002	28	1	3	140	2	2 (0)	0	0
Rituximab									
United States (multiple)	1999	53	2	4	10	10	8 (25)	6	4
Italy (Florence)	2000	54	1	2	5	3	2 (0)	1	0
United States (multiple)	2000	55	2	1	13	13	7 (14)	5	1
Italy (Albano Laziale/Rome)	2001	56	2	1	25	25	8 (13)	8	2
Germany (multiple)	2002	57	2	1	12	12	11 (36)	11	4
United States (Rochester, MN)	2002	28	1	3	140	1	1 (100)	0	0
Italy (multiple)	2002	58	2	1	7	4	1 (0)	1	0
Italy (Albano Laziale)	2002	59	1	1	7	7	3 (33)	3	2
Interferon									
United Kingdom (Newcastle)	1991	16	1	2	13	13	1 (100)	0	0
United Kingdom (Bristol)	1992	60	1	2	5	5	2 (0)	1	1
Japan (Chiba)	1992	61	1	2	5	5	3 (0)	2	0
Netherlands (Maastricht)	1994	15	1	1	21	21	21 (0)	21	0
United Kingdom (Newcastle)	1996	17	1	2	7	7	7 (14)	0	0
United Kingdom (Newcastle)	1997	18	1	4	8	8	1 (100)	1	1
Italy (Bologna)	1998	62	1	2	9	9	4 (0)	3	1
United States (Rochester, MN)	2002	28	1	3	140	1	1 (0)	0	0
Cyclosporine									
Italy (Modena)	1996	63	1	1	8	3	3 (33)	0	0
Netherlands (Rotterdam)	2001	64	1	1	20	20	10 (20)	0	0
Italy (Modena)	2002	65	1	1	12	12	8 (38)	8	1
Accessory splenectomy									
United States (Rochester, MN)	1978	66	1	4	6	6	5 (0)	4	0
Mexico (Mexico City)	1985	67	1	1	28	5	5 (60)	1	1
Australia (Camperdown)	1986	68	1	4	8	4	3 (67)	3	1
United Kingdom (London)	1990	69	1	4	8	2	1 (0)	1	0
France (Lille)	1992	70	1	4	8	5	1 (0)	0	0
Israel (Tel Aviv)	2000	71	1	4	8	5	5 (0)	0	0
Vitamin C									
Canada (Montreal, Quebec)	1988	72	1	1	11	11	3 (0)	3	2
Japan (Tokyo)	1990	73	1	1	11	11	1 (0)	0	0
France (Creteil)	1990	74	1	2	12	11	2 (0)	1	0
United Kingdom (London)	1990	75	1	4	8	8	2 (0)	2	0
Belgium (Louvain)	1990	76	1	4	14	14	3 (0)	1	0
Italy (Bologna)	1992	77	1	1	9	7	3 (0)	3	1
United States (Charleston, SC)	1993	78	1	1	12	12	2 (0)	2	0
South Africa (Cape Town)	1995	79	1	1	9	9	4 (0)	4	0
Dapsone									
France (Paris)	1993	80	1	1	27	21	3 (0)	3	1
Spain (Valencia)	1994	81	1	2	7	7	2 (0)	2	1

Appendix Table 1—**Continued**

Treatment and Country (City)	Year	Reference	Site*	Study Type†	Total Patients	Treated Patients	Platelet Counts of Eligible Patients‡		
							<50 × 10^9 cells/L	<30 × 10^9 cells/L	<10 × 10^9 cells/L
				← n →			← n (%) →		
Spain (Valencia)	1995	82	1	2	15	15	2 (0)	2	0
Italy (Milan)	1999	83	1	1	8	8	6 (0)	5	2
India (New Dehli)	2001	84	2	2	8	8	2 (50)	0	0
Anti-(Rh)D-opsonized D^+ erythrocytes									
Mexico (Mexico City)	1987	85	1	1	16	16	9 (22)	5	2
Mexico (Puebla)	1993	86	1	1	6	6	1 (100)	0	0
High-dose cyclophosphamide with stem-cell support									
United States (Bethesda, MD)	2003	87	1	1	14	9	9 (33)	9	5
Mycophenolate mofetil									
China (Jinan)	2003	88	1	1	21	21	7 (0)	7	0
Interleukin-11									
United States (New York, NY)	2001	89	1	1	7	7	7 (0)	7	5
Chlorodeoxyadenosine									
United States (La Jolla, CA)	1993	90	1	2	7	7	7 (0)	0	0
Colchicine									
United States (Ann Arbor, MI)	1984	91	1	4	14	14	3 (33)	3	0
United States (Honolulu, HI)	1986	92	1	4	7	7	1 (0)	0	0
France (Dijon)	1999	93	1	1	6	6	2 (50)	2	1
Plasma exchange									
Canada (Vancouver, British Columbia)	1981	94	1	4	6	6	1 (0)	1	1
United States (Rochester, NY)	1981	95	1	4	14	14	5 (0)	0	0
Combination chemotherapy									
United States (La Jolla, CA)	1993	96	1	4	10	6	5 (40)	4	0
WEB 2086 BS									
Germany (Giessen)	1990	97	1	1	13	13	3 (0)	3	1
Campath-1H									
United Kingdom (Cambridge)	1993	98	1	1	6	3	2 (0)	1	0
Protein A immunoadsorption									
Japan (Tochigi)	1989	99	1	2	10	6	2 (0)	2	1

* 1 = the study was performed at a single institution; 2 = the study was performed at several institutions.
† 1 = prospective cohort study of consecutive patients; 2 = prospective study with enrollment of selected patients; 3 = retrospective analysis of consecutive patients; 4 = retrospective analysis of selected patients.
‡ Patients with platelet counts less than 50 × 10^9 cells/L represent the total number of eligible patients in each article. Values in parentheses are percentage of patients with complete responses.