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REVIEW ARTICLE

Management of patients with refractory immune thrombocytopenic purpura

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Summary. In immune thrombocytopenic purpura (ITP), thrombocytopenia is a result of both increased platelet destruction and insufficient platelet production. In adults, the course is commonly chronic, but most patients never experience serious bleeding even with severe thrombocytopenia. In case series of consecutive adult patients identified at the time of diagnosis, the frequency of death from bleeding is low, < 1%. The goal of treatment is only to prevent bleeding, not to correct the platelet count to normal. All current treatments are designed to diminish the increased platelet destruction, either by immunosuppression or splenectomy. The frequency of death from complications of treatment is similar to the frequency of death from bleeding. Perhaps because of increasing recognition of both the infrequent occurrence of serious bleeding and the risks of immunosuppressive treatment and splenectomy, data from case series across the past 30 years suggest a trend toward less therapy and fewer splenectomies among patients with ITP. However treatment is necessary for patients with severe and symptomatic thrombocytopenia. Splenectomy remains the most effective treatment for ITP, with two-thirds of patients achieving durable complete remissions. Immunosuppressive agents, including rituximab and combinations of agents, may be less effective than splenectomy in achieving complete remissions and the remissions may also be less durable. New agents for patients with ITP are currently in development that enhance platelet production, rather than diminish platelet destruction. In preliminary reports, these agents have been effective in maintaining safe platelet counts in patients with chronic ITP that was refractory to splenectomy and other treatments.

Keywords: immune thrombocytopenic purpura.

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Introduction

Patients with refractory immune thrombocytopenic purpura (ITP, also known as autoimmune thrombocytopenic purpura or idiopathic thrombocytopenic purpura) are prominent in the clinical practice of hematologists. These patients may be young and in otherwise excellent health but have a perilously low platelet count that is unresponsive to all attempted treatments. Although critical bleeding is rare, even with the most severe thrombocytopenia, even a small risk seems intolerable. But treatments for ITP also have risks, such as osteoporosis caused by glucocorticoids and infections related to immunosuppression and splenectomy. The frequency of serious complications of treatment may be similar to the risk for critical bleeding. However, even though these patients may be prominent because of their difficult management, they are uncommon among all patients with ITP.

The goal of this review is to assess the current management and outcomes of patients with refractory ITP. For this review, patients are considered to have refractory ITP when they require treatment following failure to respond to initial treatment with glucocorticoids and also to splenectomy [1]. Although this definition is arbitrary, the criteria reflect important aspects of ITP. Splenectomy is the most effective and durable treatment for ITP [2], therefore patients should not be considered to be refractory until splenectomy has failed. A platelet count < 30 000 μL^{-1} may be used as a criterion for refractory ITP [1] as this is a common indication for initial treatment [3,4] and bleeding symptoms are rare in patients with platelet counts above 30 000 μL^{-1}. However following failure of splenectomy a more stringent indication for further treatment may be appropriate, requiring a lower platelet count and the presence of bleeding symptoms (Table 1). Duration of ITP for more than 3 months also may be used as a criterion for refractory ITP [1] as this is an appropriate interval to provide confidence that alternative etiologies of thrombocytopenia have been excluded and spontaneous remissions are unlikely.

Other recent reviews have addressed the pathogenesis and diagnosis of ITP as well as management [5–9]. This review will focus on ITP in adults, but the principles of evaluation and management are similar for children who have chronic ITP. Continuous re-evaluation for possible alternative etiologies of

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Table 1 An algorithm for management of patients with persistent thrombocytopenia following initial glucocorticoid treatment

Patient status	Management
Persistent thrombocytopenia following initial glucocorticoid treatment	
Platelet count > 20 000 μL^{-1} with no or only minor purpura	Observation
Platelet count < 20 000 μL^{-1} with bleeding symptoms	Splenectomy
Persistent thrombocytopenia following splenectomy	
Platelet count > 10–20 000 μL^{-1} with no or only minor symptoms	Observation
Platelet count < 10–20 000 μL^{-1} with bleeding symptoms	Rituximab, 375 mg m^{-2} wk^{-1} for 4 weeks, or intermittent dexamethasone, 10–40 mg d^{-1} for 4 days, repeated every 4 weeks or as needed, or other agents, such as azathioprine, cyclophosphamide, danazol, cyclosporine
Persistent thrombocytopenia following failure of immunosuppressive agents	
Platelet count < 10–20 000 μL^{-1} with bleeding symptoms	Investigational protocols.
Overt bleeding, such as prolonged epistaxis, mucous membrane blood blisters	Intravenous Immunoglobin (IVIG), high-dose methylprednisolone, antifibrinolytic agents, platelet transfusion for critical bleeding

thrombocytopenia, such as occult drug-induced thrombocytopenia [4,10,11] or congenital thrombocytopenia [12], is important. Measuring management intensity according to bleeding symptoms, rather than only the platelet count, is essential. Allowing the side effects of treatment to become worse than the symptoms of ITP must be avoided.

Initial treatment of ITP

Before management of refractory ITP can be addressed, the clinical course of ITP must be understood. Among all patients with ITP, who needs to be treated at first diagnosis and who can be better managed by observation alone? How many patients respond to initial treatment and how many require further treatment, such as splenectomy? How many patients fail to respond to splenectomy; how many of these patients require further treatment? Finally, how many patients die from bleeding and how many die from complications of treatment?

Glucocorticoids

Adults presenting with a platelet count < 30 000 μL^{-1} are usually treated with oral glucocorticoids. Patients who present with platelet counts higher than 30 000 μL^{-1} have been safely observed without specific treatment and without subsequent bleeding complications [3,4,13,14]. Although daily oral prednisone 1 mg kg^{-1} is a standard regimen, sustained remissions requiring no further treatment occur in only about 10–30% of patients [7,8,15]. A different initial regimen was proposed in a recent study of 125 consecutive previously untreated patients who had platelet counts of < 20 000 μL^{-1} and who were treated once with a 4-day course of oral high-dose dexamethasone (40 mg day^{-1}) [16]. Fifty-three (42%) patients had a sustained response of platelet counts more than 50 000 μL^{-1} with a median follow-up of 30 months [16], a response rate that seemed higher and more durable than with the traditional daily prednisone. This initial regimen may also have less risk for glucocorticoid side effects because of its short, defined duration [17]. A subsequent study of 18 previously untreated patients with platelet counts of 50 000 μL^{-1} or less who received 1–6 courses of high-dose dexamethasone reported that 11 (59%) had a sustained response of platelet counts more than 50 000 μL^{-1} with a median follow-up of 11 months [18]. These reports of good outcomes with high-dose dexamethasone suggest that better initial treatment regimens may decrease the occurrence of refractory ITP. However they require validation by demonstration of reproducible results and by direct comparison to daily prednisone.

Splenectomy

Following failure of initial glucocorticoid treatment, splenectomy has been the traditional next therapeutic option for over 50 years (Table 1) [7,8,15]. The number of reports of splenectomy for ITP, across many decades and many countries with consistent results (Table 2) [2] provides confidence about the benefits and risks. Of all treatments for ITP, splenectomy has the most success for achieving durable complete remissions [2]. Two-thirds of patients will respond with a normal platelet count and need no further treatment [2]. The absence of correlation between severity of thrombocytopenia and frequency of complete remissions provides confidence that remissions can be expected even in the most severely affected patients. However complications, including surgical morbidity and mortality [2], the rare occurrence of sepsis that may occur decades later [19], and a possible increased risk for atherosclerotic events [20,21] and pulmonary hypertension [22], have created concerns about the appropriateness of splenectomy. Perhaps because of concern for complications, the frequency of splenectomy has significantly decreased in the past 30 years, illustrated by comparison across sequential case series (Table 3). A trend for a decreased rate of splenectomy has also been observed across the duration of a single clinical trial in which splenectomy was part of the routine care regimen: 10 (53%) of 19 patients enrolled in 1997–1998 vs. four (22%) of 18 patients enrolled in 1999–2000 had splenectomies [23]. The decreased frequency of splenectomy may also be related to the more conservative management of ITP in recent years, with recognition that observation alone is appropriate for asymptomatic patients.

For patients with severe and symptomatic thrombocytopenia following failure of initial treatment with glucocorticoids,

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Table 2 Long-term outcomes following splenectomy: results of a systematic review of published case series. Data are adapted from the systematic review by Kojouri *et al.* [2] of all case series describing ≥15 consecutive patients who had splenectomy for immune thrombocytopenic purpura (ITP). Eighty-five case series describing 5087 patients were identified; the outcomes were consistent across 58 years (1966–2004) and 29 countries. Complete response (CR) was defined as a normal platelet count (> 150 000 μL^{-1} or as defined in the original report) achieved and maintained on no treatment for at least 30 days after splenectomy and for the duration of follow-up. Partial response was defined as a platelet count > 50 000 μL^{-1} on any measurement within 30 days after splenectomy. Death and complications were attributed to splenectomy if they occurred within 30 days of splenectomy or occurred during the hospitalization for splenectomy. Complications beyond the postoperative period, such as overwhelming sepsis, were not analyzed. The clinical importance of complications could not be assessed. 1991 was the initial year of patient accrual for case series reporting laparoscopic splenectomy

CR	3506/5087 (69%)
CR in case series with ≥5 years of follow-up	779/1159 (67%)
Relapse following CR (median follow-up, 33 months; range, 3–153 months)	15% (range, 0–51%) (correlation of relapse rate with duration of follow-up: $r_s = 0.275$, $P = 0.059$)
Surgical complications	
Death	
Laparotomy	48/4955 (1.0%)
Laparoscopy	3/1301 (0.2%)
(Laparotomy with patient accrual since 1991)	1/134 (0.75%)
Complications	
Laparotomy	318/2465 (12.9%)
Laparoscopy	88/921 (9.6%)

splenectomy may be the most effective treatment option. However, because of the risks associated with splenectomy a more stringent indication of a platelet count < 20 000 μL^{-1} may be appropriate (Table 1). Because of the effectiveness of splenectomy, patients may not be considered to be refractory until splenectomy has failed.

Frequency of refractory ITP

Although patients with refractory ITP may be prominent in the practice of hematologists, they are not common. Table 3 summarizes data from six recent large case series of consecutive patients with ITP. In the most recent case series (case series 6), no patients required treatment after splenectomy even though seven (23%) of 30 splenectomized patients had only a partial response [4]. In three other case series (case series 1, 2, and 4), 9–30% of patients who had had splenectomy required further treatment [3,14,24]. Pooling the experience of these four case series (case series 1, 2, 4, and 6), 75 (20%) of 375 splenectomized patients had further treatment [3,4,14,24]. Among the case series for which data are available for rates of splenectomy (case series 1, 2, 3, and 6), 250 (30%) of the 824 patients who were initially diagnosed with ITP had a splenectomy. Taken together, these data suggest that < 10% of patients who are initially diagnosed with ITP may eventually be considered to be refractory by the definition of a requirement for further treatment following splenectomy.

Mortality of ITP

The potential for benefit with any treatment for ITP must be measured against the risks. This consideration is critical for patients with ITP because deaths caused by bleeding are rare and may be similar to the frequency of treatment-related deaths. In the five case series that described consecutive patients with a new diagnosis of ITP (Table 3, case series 1–4, 6), the mortality from bleeding was only nine (0.8%) of 1079 patients. The range of reported mortality rates in these five case series was 0.3–1.3% [3,4,13,14,24]. These data may overestimate deaths attributable to ITP as some patients who died from bleeding had other risk factors that may have contributed to the hemorrhage, such as

Table 3 Data are presented from six recent case series of consecutive patients that provide outcome data. Case series 1–4 and 6 are consecutive patients with a new diagnosis of ITP; Case series 5 reports consecutive patients referred for treatment following failure of splenectomy (see Appendix 1 for details of case series)

	Case series					
	1 [3]	2 [14]	3 [13]	4 [24]	5 [25]	6 [4]
Patient accrual (years)	1974–1994	1963–1997	1982–1989	1985–1994	1986–1998	1993–1999
Duration of follow-up, years (median)	10.5	10	3	7.5	9.2	5
Patients with initial diagnosis of ITP	152	310	117	NR	NR	245
Patients with initial platelet count < 30 000 μL^{-1}	124 (82%)	230 (74%)†	49 (42%)‡	NR	NR	191 (78%)
Patients with splenectomy	78 (51%)	109 (30%)	33 (28%)	158	NR	30 (12%)
Patients with further treatment after splenectomy (% of splenectomized patients)	14 (9%)	33 (30%)	NR	28 (18%)	105	0
Response (% of all patients)*:						
CR	97 (76%)	NR	82 (70%)	148 (94%)	51 (49%)	155 (66%)
PR	23 (18%)	NR	28 (24%)	6 (4%)	24 (23%)	64 (27%)
NR (or on continuing treatment)	8 (6%)	34 (11%)	7 (6%)	4 (2%)	30 (28%)	17 (7%)
Deaths (% of all patients):						
Because of bleeding	2 (1.3%)	1 (0.3%)	1 (0.8%)	2 (1%)	11 (10%)	3 (1.2%)
Treatment-related	4 (2.6%)	NR	NR	0	6 (6%)	1 (0.4%)
Unrelated to ITP	15	NR	NR	0	32	21
Unknown cause	3	NR	NR	0	0	2

*In these case series, a complete response (CR) was usually defined as a platelet count > 100 000 μL^{-1} on no treatment; a criterion for duration of the platelet count response was not described. A requirement for continuing treatment or a response to only a platelet count of 30 000–100 000 μL^{-1} was usually designated as a partial response (PR). The remaining patients, designated as no response (NR), were usually described as refractory, with platelet counts < 30 000 μL^{-1}. †Data presented for platelet counts < 50 000 μL^{-1}, rather than < 30 000 μL^{-1}. ‡In addition to these 49 patients, other patients presented with platelet counts < 30 000 μL^{-1} but received treatment.
CR, complete response; NR, no response (data not reported); PR, partial response; ITP, immune thrombocytopenic purpura.

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non-Hodgkin's lymphoma or warfarin therapy [4]. In the case series of McMillan and Durette [25], (case series 5), 11 (10%) of 105 patients died from bleeding, but these patients were selected by referral to the Scripps Research Institute for treatment following failure of splenectomy. This high mortality appears to suggest that intensive treatment following failure of splenectomy is appropriate, yet a 6% treatment-related mortality is also reported in this case series [25]. The frequency of treatment-related deaths is difficult to assess because cytotoxic agents may also contribute to thrombocytopenia and increase the risk for death from bleeding, deaths that may not have been attributed to the treatment.

In the case series by Portielje *et al.* the number of patients who died from infections related to treatment was greater than the number of patients who died from bleeding [3]. Among their 152 patients followed for a median of 10.5 years (Table 3, case series 1), two patients died from bleeding; both were young women, ages 35 and 40 years, who had intracerebral hemorrhage when their platelet counts were 2000 and 3000 μL^{-1}. Four patients died from complications of treatment when their platelet counts were normal: an 83-year-old man died from cytomegalovirus infection following treatment with glucocorticoids and splenectomy; a 65-year-old woman died from Gram-negative sepsis after 3 months of glucocorticoid treatment; an 86-year-old woman died of Gram-negative sepsis after 3 months of treatment with glucocorticoids and immunosuppressives; a 20-year-old man died from pneumococcal sepsis 2.5 years after a splenectomy, despite previous pneumococcal immunization.

Management of patients with refractory ITP: assessment of benefits and risks

Other than for splenectomy, reports of benefits and risks of treatments for patients with ITP are surprisingly rare. There are no studies comparing results with one treatment to another and no studies comparing treatment with no treatment. A systematic review of all English-language publications from 1966 through 2003 to search for treatment of patients who had had ITP for more than 3 months, had had splenectomy, and had a platelet count < 30 000 μL^{-1} identified 71 articles that described 365 patients treated with 21 different therapies [1]. For patients who had a platelet count < 10 000 μL^{-1}, the patients who are actually at risk for serious bleeding, there were 44 articles describing only 112 patients treated with 18 different therapies [1]. That there are so few reported patients may at first seem unbelievable. But in most articles describing treatment of ITP, patients with or without splenectomy and with varying durations of ITP and severity of thrombocytopenia are reported together. In these articles, individual patient data often cannot be determined, because group data are reported as mean values and ranges. The most important information for physicians, data on the outcome of patients with the most severe thrombocytopenia, is not often described. Even when individual patient data are reported, bleeding symptoms are rarely described. Most reports only describe platelet count responses without comment on benefit for the symptoms of ITP.

Table 4 Management of adult patients following failure of splenectomy: results of a systematic review of published cases series. Data are adapted from the systematic review of individual patient data by Vesely *et al.* [1] of all case series describing greater than five patients with ITP that contained at least one patient who met criteria for an adult with chronic, refractory ITP: age > 16 years old, duration of ITP > 3 months, prior splenectomy, and platelet count < 50 000 μL^{-1}. Patients were subsequently analyzed according to the severity of their thrombocytopenia: < 50 000 μL^{-1}, < 30 000 μL^{-1}, and < 10 000 μL^{-1}. In this Table, data are presented for eight selected treatments and for the two most severe and clinically important levels of thrombocytopenia. The number of patients (n) for each treatment at each level of thrombocytopenia represents all patients who could be identified with individual interpretable data. Complete response is defined as maintaining a normal platelet, > 150 000 μL^{-1}, on no treatment for the duration of observation

Treatment	Pre-treatment platelet count ($\times 10^3$ μL^{-1})	Patients (n)	Complete response (%)
Accessory splenectomy	< 30	9	33
	< 10	2	100
Azathioprine	< 30	53	19
	< 10	16	25
Vincristine/vinblastine	< 30	34	6
	< 10	8	0
Cyclophosphamide	< 30	28	39
	< 10	20	40
High-dose cylcophosphamide with autologous stem cell support	< 30	9	33
	< 10	5	40
High-dose dexamethasone	< 30	46	11
	< 10	11	27

The results for selected treatments from this systematic review are presented in Table 4. The number of patients at each pre-treatment platelet count level, < 30 000 μL^{-1} or < 10 000 μL^{-1} is presented, as well as the percentage of patients having a complete response. Even though the important goal of treatment is only to achieve a safe platelet, not necessarily a normal platelet count, complete responses are presented here and in the subsequent discussion because they can be clearly defined. Partial responses, that may be only transient and may only occur with continuing treatment, are more difficult to interpret. Also patients who are described as not responding may still have some value from the treatment, as only a small increase in platelet count may provide substantial freedom from bleeding symptoms.

The remarkable observation from this systematic review was the absence of information to guide clinical decisions. The most important information would be description of outcomes of patients with severe and symptomatic thrombocytopenia: the patients who most need treatment. Yet these patients are the least represented among all case series. In addition, for many of the agents reported, only a few articles and sites provided most of the patients [1]. For some treatments, all complete responses were in only one of many reports [1]. These observations make interpretation of published reports on treatment of refractory ITP even more difficult to interpret. Although the results of this systematic review cannot provide objective evidence to determine which treatments may be most effective, or even whether any treatment is more effective than observation, from this review we can clearly understand why there is no consistent approach to the treatment of patients with refractory ITP, and why management of these patients remains empirical.

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Management decisions must include assessment of lifestyle. Younger athletic patients or patients whose profession involves risk for trauma may require a higher platelet count. Older more sedentary patients may do well with much lower platelet counts, though some observations suggest that bleeding risks are greater in older patients [13,26,27]. Perhaps more important is the presence of other medical conditions that could increase the risk for serious bleeding, such as hypertension and symptoms of cerebrovascular disease. Also, some patients may be at greater risk for opportunistic infections resulting from immunosuppressive therapy. All of these considerations together emphasize the critical importance of individualized treatment, and the importance of shared decisions between the physician and patient (e.g. see 'Crystal's Story', http://moon.ouhsc.edu/jgeorge; accessed 4 May 2006). For some patients, quality of life on no treatment is far better than with any of the commonly prescribed treatments for refractory ITP.

Management of refractory ITP: currently available treatments

Once a decision for intervention is made, the choice is often among the following regimens [6,8].

Glucocorticoids

In some patients, the platelet count can be maintained in a safe range on very low doses or intermittent doses of glucocorticoid that do not cause distressing symptoms. However even low doses of glucocorticoid, within the range of physiologic cortisol levels, may accelerate the development of osteoporosis [28].

Removal of accessory spleens

Although removal of an accessory spleen has been described for decades as an appropriate treatment for patients with refractory ITP, there are few published data to support this practice. Most published case reports are in children, who seem to respond better than adults to all treatments, and who also seem to have a steady rate of spontaneous remission [29]. Other published data are on patients who have had ITP for < 3 months, and therefore may more likely have a spontaneous remission. Only two patients could be identified in all published reports who had pre-treatment platelet counts < 10 000 μL^{-1} and had had ITP for longer than 3 months (Table 4) [1]. Therefore, the potential benefit from removal of an accessory spleen may not exceed the risks from surgery.

Rituximab

Rituximab is currently the most popular immunosuppressive agent used for treatment of patients with refractory ITP. Although rituximab is only approved for use in non-Hodgkin's lymphoma, it is widely used for many autoimmune disorders [30]. Rituximab is popular because of its relative safety, without apparent risk for marrow suppression. Rituximab is a humanized monoclonal anti-CD20 antibody that results in depletion of the immunoglobulin-producing B cells but has negligible effect on circulating IgG serum levels [31]. Serious reactions are rare, but include serum sickness, hypotension, bronchospasm, pulmonary infiltrates with acute respiratory distress syndrome, and cardiogeneic shock.

Table 5 Results of rituximab treatment for adults ITP: 1997–2004. Data adapted from Arnold *et al.* [32] who have reported in an abstract a systemic review of published reports on rituximab for ITP, 1997–2004. Patients were > 15 years old. All studies were case reports, case series, or single-arm cohorts. No comparative trials of either a randomized or non-randomized design have been published. In most studies, rituximab was administered as 4 weekly infusions of 375 mg m^{-2}. Complete response was not defined and duration of follow-up was not described

Number of reports	39
Number of patients	
Total patients	365
Patients failing splenectomy	195 (53%)
Patients failing danazol, immunosuppressive, and/or cytoxic agents	100 (27%)
Complete response (calculated for the 17 reports that described ≥five patients)	48%

The data for efficacy of rituximab are presented in Table 5. Although only currently published in abstract form, this systematic review of the literature is the most complete summary of rituximab treatment for ITP [32]. Thirty-nine studies were identified, including 21 full-text articles, describing a total of 357 patients. All of the studies were case reports or cohorts; none was a comparative trial of either a randomized or non-randomized design. Approximately half of the patients had failed splenectomy and one-quarter had failed other treatments. Approximately half of patients were described as having a complete response, with a platelet count more than 100 000 μL^{-1}. However, the presence of concomitant or continuing medications was not clear [32] and the duration of experience with rituximab has been limited. These data are comparable to a more recently published prospective cohort study of 36 consecutive children, all of whom had initial platelet counts < 30 000 μL^{-1} [31]. Eleven (31%) of the 30 children responded with a sustained platelet count over 100 000 μL^{-1} for at least four consecutive weeks [31].

Cyclophosphamide

Uncontrolled case series of selected patients have reported complete responses in 20–40% of patients following several months of treatment with either daily oral cyclophosphamide or intermittent intravenous doses of approximately 1000 mg m^{-2} repeated at 4 weeks intervals for several doses [1,33–35]. However the published experience with cyclophosphamide in patients with severe refractory thrombocytopenia is very small.

Azathioprine

Similarly, uncontrolled case series of selected patients have reported that approximately 20% of patients may achieve a complete response with a daily oral dose of azathioprine 1–2 mg kg^{-1} for several months [1,34,36].

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Vinca alkaloids

Vinblastine or vincristine, administered either by intravenous bolus or infusion, have comparable results. Transient increases of the platelet count are frequently reported but durable complete remissions are rarely described [1].

Combination chemotherapy

Reports have described combination regimens adapted from the treatment of patients with malignant lymphoma, and have described complete responses [37,38]. A familiar and well-tolerated regimen is the combination of intravenous bolus cyclophosphamide and vincristine on day 1 and intravenous methylprednisolone, 1000 mg, on days 1–3 [39]. Patients have also been treated with more intensive chemotherapy, with or without peripheral blood stem cell support, also with descriptions of complete responses [1,37,40,41].

In the reports of patients with immunosuppressive agents, there are occurrences of death from bleeding. Although these hemorrhagic deaths are typically interpreted as indicating the severity of disease and necessity for treatment, the possibility exists that immunosuppressive treatments may also be myelosuppressive, resulting in more severe thrombocytopenia and potentially increasing the risk for severe bleeding.

Danazol

Although danazol may cause sustained platelet count responses while treatment is continued, durable responses after treatment is stopped are rarely described [1]. Danazol may be more effective when given together with immunosuppressive agents, and danazol may have the added benefit of diminishing menorrhagia [8]. Danazol may also cause acute thrombocytopenia [42,43].

Helicobacter pylori *eradication*

Eradication of *H. pylori* has been associated with increased platelet counts in some case series. However the results are not consistent, with some reports describing that a majority of patients responded with increased platelet counts following *H. pylori* eradication by an antibiotic regimen [44] while other reports describe no responses [45,46].

Other agents

Many other treatments have been used in patients with refractory ITP, all with anecdotes of success but none with evidence for efficacy [1]. These treatments include interferon, cyclosporine, mycophenolate mofetil, dapsone, etanercept, colchicine, and campath-1H [1,6,8,9].

In summary, many, perhaps most patients with severe and symptomatic refractory ITP may not respond to any of the currently available treatments. In spite of this, as documented in Table 3, deaths from bleeding are rare. However because the quality of life of patients with continuing severe thrombocytopenia is poor [47], new treatment strategies are needed, and several agents are in clinical development.

Management of refractory ITP: investigational treatments

Thrombopoietin mimetic agents

A new approach to treatment is based on increasing platelet production rather than decreasing the rate of platelet destruction. This concept is based on the observation that many patients with ITP have less than maximal platelet production [48] and relative endogenous thrombopoietin deficiency [49,50]. The lack of compensatory increased platelet production may be related to the effect of antiplatelet autoantibodies on maturing megakaryocytes [51,52]. The relative endogenous thrombopoietin deficiency, in contrast to patients with aplastic anemia, is related to adsorption of thrombopoietin by the normal or increased numbers of marrow megakaryocytes [49,50]. An initial report described benefit in three of four patients with chronic ITP [53].

Sequential clinical trials with one thrombopoietin mimetic agent have been described in a series of abstracts over the past 3 years [54–56]. This investigational agent, described as AMG 531, is a synthetic molecule linked to domains that bind to the thrombopoietin receptor and result in the same *in vitro* intracellular signaling and megakaryocyte growth stimulation as endogenous thrombopoietin [57]. Studies of patients with ITP who had platelet counts $< 30\,000\ \mu L^{-1}$ (or $< 50\,000\ \mu L^{-1}$ in patients on a stable dose of glucocorticoid), ITP for more than 3 months, and who had failed at least one prior treatment have demonstrated a dose-related response with some patients exceeding a platelet count of $50\,000\ \mu L^{-1}$ at a dose of $2\ \mu g\ kg^{-1}$ and most patients achieving the target goal of a platelet count over $50\,000\ \mu L^{-1}$ and at least twice the pretreatment platelet at a dose of $10\ \mu g\ kg^{-1}$ [54,55]. All patients who have participated in one of the clinical trials are eligible for an extension study of weekly subcutaneous administration with dose adjustment and home administration when stable safe platelet counts were achieved. A preliminary report of 23 patients on this extension study documented that 21 (91%) responded with a doubling of their baseline platelet count and achieving a platelet count of more than $50\,000\ \mu L^{-1}$ (Table 6) [56].

Another thrombopoietic mimetic agent in clinical trials is eltrombopag (SB-497115-GR), a non-peptide small molecule that binds to the thrombpoietin receptor, resulting in signal-transduction responses and megakaryocyte development similar to thrombopoietin [58]. Daily oral administration results in a dose-related increase in platelet counts in healthy subjects [59] and in patients with ITP (Table 6) [60].

Adverse affects to thrombopoietin have been negligible. One patient developed increased marrow reticulin with a leukoerythroblastic reaction that improved within several months after stopping the AMG 531 [61]. This reaction is comparable to the increased marrow reticulin observed in

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Table 6 Platelet responses to thrombpoietin receptor agonists that increase platelet production: preliminary data. Data for AMG 531 are adapted from Bussel *et al.* [56] AMG 531 is an investigational agent produced by Amgen, Inc., Thousands Oaks, CA, USA and is currently in Phase III clinical trials. Data for SB-497115-GR (eltrombopag) are from a Corporate Friday Symposium at the 47th Annual Meeting of the American Society of Hematology and published online [60]. SB-497115-GR is an investigational agent produced by GlaxoSmithKline plc, Brentford, UK

AMG 531
26 patients with platelet counts < 30 000 μL^{-1}, or < 50 000 μL^{-1} if on steroid treatment, were treated with weekly subcutaneous injections of adjusted doses for up to 24 weeks
21 (81%) had had splenectomy
Mean baseline platelet count: 18 500 μL^{-1}
21 (81%) responded (defined by doubling the platelet count and > 50 000 μL^{-1})
Seven (27%) had platelet count responses that exceeded the target range of 50 000 μL^{-1} to 400 000 μL^{-1}
Six patients were initially on steroid treatment: three discontinued, two decreased their dose.
One related severe adverse event: reversible marrow reticulin formation
SB-497115 (eltrombopag)
97 patients with platelet counts < 30 000 μL^{-1} were treated with daily oral doses of 30, 50, or 75 mg day^{-1}, or placebo, for 6 weeks
Most patients treated with doses of 50 or 75 mg day^{-1} responded with platelet counts > 50 000 μL^{-1} (P < 0.001 compared to placebo)

eight of 13 patients who were treated with a different thrombopoietin agent following induction therapy for acute myeloid leukemia [62]. The reticulin formation is presumably related to the megakaryocyte hyperplasia induced by the thrombopoietin agents and secretion of platelet-derived growth factor [62].

Management of refractory ITP: control of bleeding in patients who do not respond to treatment

In patients whose platelet count does not respond to any treatment and who have significant bleeding symptoms, non-specific measures to control bleeding may be effective. Aspirin and non-steroidal anti-inflammatory drugs are avoided. Birth control pills may control menorrhagia. Antifibrinolytic agents, such as aminocaproic acid and tranexamic acid, may control chronic bleeding [63,64]. In patients whose platelet counts respond to treatment, but only briefly, intermittent short courses of prednisone or dexamethasone, or intermittent treatment with intravenous immunoglobulin may be beneficial.

However most unresponsive patients eventually do well, or at least are able to remain active and function normally on no treatment (e.g., see 'Christy's Story' http://moon.ouhsc.edu/jgeorge; accessed 4 May 2006).

Emergency management for critical bleeding

Life-threatening bleeding requires immediate administration of platelet transfusions, intravenous methylprednisolone (1000 mg), and intravenous immunoglobulin [15]. Although platelet count increments may be small and transient after a platelet transfusion, platelet counts do increase in many patients and most patients have a hemostatic benefit [65,66]. For continued bleeding, intravenous factor VIIa may be effective [67,68].

Conclusions

The occurrence of refractory ITP is uncommon and the occurrence of death from bleeding in ITP is rare. There are no data to guide management decisions, to confidently assess whether one form of treatment is better than another, or whether treatment is better than observation. Therefore reserving treatment for patients with bleeding symptoms may be the current best management. For many patients with ITP, their experience with the side effects of multiple treatments has been worse than any bleeding symptoms that they have experienced. Intermittent treatment with glucocorticoids, such as 4 days of dexamethasone given as needed, may be sufficient to treat symptoms of severe thrombocytopenia. More durable responses may be achieved with rituximab, cyclophosphamide, or combinations of agents. New treatments in development for ITP may provide effective and more tolerable options for patients with refractory ITP. The principal rule for management of patients with refractory ITP is to never allow the side effects of treatment to become worse than the symptoms of the ITP.

Disclosure of Conflict of Interest

Dr George has been paid as a consultant and for clinical trial research for ITP by Amgen, Inc.

Appendix 1

Case series 1 Patients in the case series by Portielje *et al.* [3] were from the Leiden University Medical Center, the Netherlands, and were identified retrospectively by review of the bone marrow examination registry and diagnosis data banks. Patients had platelet counts < 100 000 μL^{-1} and were ≥15 years old.

Case series 2 Patients in the case series by Vianelli *et al.* [14] had been diagnosed and treated at the 'Seragnoli' Institute of Hematology and Oncology in Bologna, Italy. Patients had platelet counts < 150 000 μL^{-1} for at least 6 months. Although the cohort is described as adult patients, the age range included children as young as 6 years old.

Case series 3 Patients in the case series by Cortelazzo *et al.* [13] had been hospitalized at the Ospedali Riunita di Bergamo in Bergamo, Italy. Patients had platelet counts < 100 000 μL^{-1} for at least 6 months and were ≥16 years old.

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Case series 4 For the case series by Bourgeois *et al.* [24], the data in this table describe only the outcomes of the 158 adult patients (age > 15 years) who had a splenectomy. The number of adults among the total 255 patients was not reported.

Case series 5 In the case series by McMillan and Durette [55], the 105 patients were referred to the Scripps Research Institute, La Jolla, CA, USA for treatment of thrombocytopenia following splenectomy; therefore it may be assumed that these selected patients were severely affected although bleeding symptoms were not described. Patients were ≥14 years old.

Case series 6 Patients in the case series by Neylon *et al.* [4] were identified by registration with the Northern Health Region of England, UK. Patients were ≥16 years old, had platelet counts < 50 000 μL^{-1}, and had a bone marrow biopsy.

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