Morbidity and mortality in adults with idiopathic thrombocytopenic purpura

Johanna E. A. Portielje, Rudi G. J. Westendorp, Hanneke C. Kluin-Nelemans, and Anneke Brand

To study outcomes of adults with idiopathic thrombocytopenic purpura (ITP), we performed a follow-up study in a cohort of 152 consecutive patients who were treated according to a well-defined algorithm. Long-term outcomes were determined relative to the response 2 years after diagnosis, because most (93%) patients who ultimately attained platelet counts above 30.0 × 10^9/L (30 000/μL) did so within this time frame. Complete follow-up for mortality could be studied in 99% of patients and for morbidity in 95% of patients, with a mean of 10.5 years. Within 2 years after diagnosis, 4 patients died, 2 were lost to follow-up, and 12 were reclassified as having secondary immune thrombocytopenia. Of the remaining 134 patients, 114 (85%) had obtained platelet counts above 30.0 × 10^9/L while all therapies had been discontinued. These patients had a long-term mortality risk equal to the general population. Twelve of 134 patients (9%), all with severe thrombocytopenia, had refractory disease and suffered a mortality risk of 4.2 (95% confidence interval, 1.7-10.0). Bleeding and infection equally contributed to the death of these patients. Another 8 patients (6%) had platelet counts above 30.0 × 10^9/L while on maintenance therapy. Similar to patients with refractory disease, these latter patients had considerably increased ITP-related hospital admissions, but mortality was only slightly higher than in the general population. In conclusion, most adults with ITP have a good outcome with infrequent hospital admissions and no excess mortality. The absence of gross morbidity and mortality in patients with moderate thrombocytopenia supports clinical practice refraining from further treatment. (Blood. 2001;97:2549-2554)

Introduction

Morbidity and mortality in adult patients with idiopathic thrombocytopenic purpura (ITP) have seldom been studied systematically. The several patient series reported in the literature have accrued different types of patients, differ in follow-up, and therefore do not permit drawing conclusions on morbidity and mortality in the patient population with ITP at large.[1-12] Most studies are primarily concerned with the success or failure of different therapies to increase platelet levels, which is a surrogate marker of morbidity. Moreover, although many studies address hemorrhagic events and deaths during follow-up, the complications of medical and surgical therapies of the disease have not been consistently taken into account, and therefore morbidity and mortality of ITP may have been underestimated.

Patients with refractory disease are expected to have the worst outcome. The lack of information on the course of refractory disease prohibited treatment recommendations in the guidelines for diagnosis and treatment of ITP of the American Society of Hematology for patients with ITP who do not respond to treatment with corticosteroids and splenectomy.[13,14]

To determine the mortality and morbidity of adults with ITP, we followed all patients with ITP, with emphasis on refractory disease, referred to the Departments of Hematology and Internal Medicine of the Leiden University Medical Center, for 20 years. Patients were mostly treated according to a well-defined algorithm. Outcomes were studied relative to the response to treatment that was attained 2 years after diagnosis.

Patients and methods

Patients

Patients with a probable diagnosis of immune thrombocytopenia aged 15 years or older at diagnosis were identified from 3 data files. First, patients newly diagnosed between January 1, 1974, and January 1, 1980, were extracted from the bone marrow examination registry. This registry contains the descriptions of all bone marrow examinations performed in our hospital. It also contains the descriptions of revisions of bone marrow preparations from patients who were referred from other hospitals. To verify the diagnosis, all charts were studied from patients with thrombocytopenia and normal or increased numbers of megakaryocytes in an otherwise normal bone marrow. Secondly, patients newly diagnosed between January 1, 1980, and August 1, 1994, were extracted from the hospital's central data bank on diagnoses. Thirdly, patients newly diagnosed between January 1, 1980, and August 1, 1994, were extracted from the Department of Hematology's data bank on diagnoses. Together, these data banks contain virtually all patients with immune thrombocytopenia seen in the outpatient clinics and in the hospital.

To verify the diagnosis, patients' charts were searched for information concerning medical history, referral from or to other hospitals, concomitant diseases, presenting symptoms, bone marrow findings, and medication at the time of presentation. ITP was defined by (a) a platelet count below 100.0 × 10^9/L (100 000/μL) of peripheral blood, (b) normal or increased megakaryopoiesis on bone marrow examination, and (c) the absence of clinically apparent associated conditions or causes of thrombocytopenia. Moderate thrombocytopenia was defined as an initial platelet count between 30.0 × 10^9/L (30 000/μL) and 100.0 × 10^9/L without a decrease below 30.0 × 10^9/L during the first 3 months of observation. Severe thrombocytopenia was defined as a platelet count below 30.0 × 10^9/L at

From the Departments of Internal Medicine, Clinical Epidemiology, and Hematology, Leiden University Medical Center, The Netherlands.

Submitted May 23, 2000; accepted December 11, 2000.

Reprints: J. E. A. Portielje, Daniel den Hoed Kliniek, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands; e-mail: jportiel@worldonline.nl.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 U.S.C. section 1734.

presentation or an initial count between 30.0×10^9/L and 100.0×10^9/L with a subsequent decrease below 30.0×10^9/L during the following 3 months.

Out of a series of 213 patients with a presumptive diagnosis of immune thrombocytopenia, 59 were excluded from the main analysis for the following reasons. Thirteen patients were known to have had an infection that can cause thrombocytopenia (human immunodeficiency virus, Epstein-Barr virus, rubella, toxoplasma, or viral hepatitis). From patients with concomitant infections other than human immunodeficiency virus, all but one patient (with Epstein-Barr virus) had normalization of platelet counts within 3 months. Twenty patients had been exposed to a drug known to be associated with thrombocytopenia. They were excluded from the study population when normalization of platelet counts was confirmed after cessation of the drug. Twenty-six patients, who at the time of diagnosis of thrombocytopenia had a concomitant systemic disease associated with thrombocytopenia, were considered to have a secondary immune thrombocytopenia. Two patients were lost to follow-up due to emigration. Hence, the study population with ITP comprised 152 patients with a diagnosis established between January 1, 1974, and August 1, 1994 (Table 1). Seventy-three patients were primary referrals. Seventy-nine patients were referred to our institution after the diagnosis had been established in another hospital, ie, secondary referrals.

Therapy and response

Most patients were treated according to the following algorithm.

First-line treatment. This consisted of oral prednisone (1 mg/kg/d) for 3 to 6 weeks, followed by a tapering off period of maximally 1 year with subsequent withdrawal. Indications for splenectomy were no platelet response after at least 6 weeks of prednisone, one or more recurrences after withdrawal of prednisone, or requirement of maintenance prednisone treatment (> 0.10 mg/kg).

Second-line treatment. If no response occurred after splenectomy, prednisone was reintroduced (prednisone maintenance therapy) or therapy was changed to immunosuppressive therapies, danazol, or high-dose dexamethasone. The therapeutic approaches for second-line therapies were in line with the therapeutic guidelines as given by McMillan, except for the effect of danazol, which was awaited for 2 instead of 6 months.[15] Therapy with intravenous gamma globulin was reserved for interventions during serious bleeding episodes that persisted on maintenance drug therapy and to raise platelets before splenectomy or other surgery.

Other treatment. Seventeen patients were not treated according to this algorithm. When prednisone failed to induce a sustained response, they were not treated with splenectomy but with vincristine (11 patients) or irradiation of the spleen (1 patient). In 3 other patients, platelet counts increased to normal values on prednisone but, instead of tapering off, the drug was continued at low doses for more than 3 years. Two additional patients were treated with prednisone and subsequently with immunosuppressives because they developed an autoimmune disease during the first 2 years of follow-up.

Complete response was defined as a platelet count of more than 100.0×10^9/L without therapy for at least 2 months. Partial response was defined as a platelet count of more than 30.0×10^9/L without therapy for at least 2 months. Response to maintenance therapy was defined as a platelet count of more than 30.0×10^9/L during drug therapy. No response was defined as a platelet count of fewer than 30.0×10^9/L with or without therapy.

Table 1. Characteristics of 152 patients with ITP as initial diagnosis

Characteristics	All patients (n = 152)
Sex, no. of patients (%)	
Male	56 (37)
Female	96 (63)
Mean age, y (range)	
Males	41 (15-85)
Females	37 (16-86)
Thrombocytopenia,* no. of patients (%)	
Moderate	28 (18)
Severe	124 (82)
Referral, no. of patients (%)	
Primary	73 (48)
Secondary	79 (52)
Presenting symptoms, no. of patients (%)	
No hemorrhagic symptoms	28 (18)
Hemorrhagic symptoms	124 (82)
Skin or mucosal bleeding only	89
Bleeding from genitourinary or gastrointestinal tract	32
Persistent bleeding after surgery	3

*Moderate thrombocytopenia = platelet counts between 30.0×10^9/L and 100.0×10^9/L (30 000 and 100 000/μL); severe thrombocytopenia = platelet counts below 30.0×10^9/L.

Follow-up

For each patient, the observation period started on the day of initial diagnosis. Patients were followed and analyzed until the observation period ended on August 1, 1996, or until death (due to any cause). Medical charts were studied for information concerning treatment, response, treatment complications, and hospital admissions. We also assessed the occurrence of newly diagnosed malignancies, systemic autoimmune diseases, or lymphoproliferative disorders. Of all patients with a partial or complete response at last follow-up (last medical control before August 1, 1996, or death), 93% had attained this response within the first 2 years of observation. We therefore decided to study long-term morbidity and mortality depending on the response to therapy 2 years after initial diagnosis.

Through the Dutch municipal registrations, we ascertained whether patients with ITP were alive on August 1, 1996, or had died within the observation period. From patients who had died, information concerning treatment, hospital admissions, and the cause of death was obtained from the medical charts, the hospital's computed registry, the patient's home practitioner, and medical specialists who had provided care outside our hospital. Questionnaires were sent to all patients still alive, and telephone calls were made to nonresponders (ultimate response 91%). The questionnaire principally aimed to obtain complete information on the course of disease when patients were no longer visiting our hospital. It contained questions about symptoms at initial presentation, treatment, treatment duration, splenectomy complications, hospital admissions, relapses, and other reasons to seek medical advice after the diagnosis of ITP. When the answers contained information on events or treatment that had occurred outside our hospital, confirmation was obtained from the physician who had provided the care.

The incidence of hospital admissions was assessed. Admissions were defined as related or unrelated to ITP. Admissions were defined as related if they were due to (a) analysis or treatment of thrombocytopenia or hemorrhage, (b) infectious diseases related to immunosupressive treatment, (c) other complications of therapy, (d) platelet-augmenting therapies preceding surgical interventions other than splenectomy, or (e) delivery. All other admissions were considered unrelated. First admissions, during which the diagnosis of ITP was established, were not included in the analysis. The occurrence of complications of splenectomy during the observation period was assessed.

Statistical analysis

The total mortality of patients with ITP (all causes) was compared with that of the general Dutch population standardized for age, gender, and calendar period. The expected number of deaths among patients was calculated by multiplying the number of person-years per category of age, gender, and calendar period with the corresponding mortality rates of the Dutch population. The standardized mortality ratio (SMR) was calculated by dividing the observed number of deaths by the expected number of deaths. The 95% confidence interval (CI) of the SMR was calculated assuming a Poisson distribution for the observed number of deaths.

Results

Patient series

Baseline characteristics of the cohort of 152 patients with an initial diagnosis of ITP are shown in Table 1. The mean age at diagnosis was 39

years, and more patients were female. Most patients presented with severe thrombocytopenia and purpura or petechiae. During the first 2 years, 12 patients developed symptoms of systemic or discoid lupus erythematosis (6), rheumatoid arthritis (1), lung carcinoma (1), chronic colitis (2), non-Hodgkin's lymphoma (1), or a nonclassified serositis and nephritis (1) and were reclassified as having secondary immune thrombocytopenia. They did not distinguish themselves at the time of initial diagnosis, although a higher percentage presented with moderate thrombocytopenia (42%).

Four patients with severe thrombocytopenia at diagnosis died during the first 2 years of observation. A 40-year-old woman, with a platelet count of 3.0×10^9/L (3000/μL) shortly before death, died from intracerebral bleeding. A 65-year-old woman, with normal platelet counts before death, died due to a gram-negative sepsis after 3 months of corticosteroid treatment. An 86-year-old woman, with a platelet count of 63.0×10^9/L (63 000/μL) before death, died of a gram-negative sepsis after having been treated for 3 months with corticosteroids and immunosuppressives. An 83-year-old man with normal platelet counts before death had been treated for several months with corticosteroids when a splenectomy, complicated by a myocardial infection, was performed. Postoperative recovery was slow, and he ultimately died from a cytomegalovirus pneumonia. All had normal leukocyte and neutrophil counts directly before death.

Two patients with severe thrombocytopenia, alive at last follow-up, visited our institution only once, and we did not succeed in obtaining information on treatment and hospital admissions.

Data on long-term survival were obtained for 99% of patients for a mean of 10.5 years (median 9.4 years; range 2 months-22.6 years). Twenty patients died during long-term follow-up. Using questionnaires, medical charts, and communications with treating physicians, we could obtain complete follow-up for morbidity for 110 of the 114 patients who were alive at the end of follow-up and from 18 of 20 patients who died during the follow-up.

Hematologic response

Table 2 shows the hematologic response to therapy 2 years after the diagnosis. Of 124 patients with severe thrombocytopenia, 82 attained a complete response and 9 a partial response. First-line therapy contributed to 84 of these 91 responses. Half of the patients with severe thrombocytopenia, who attained a complete response on prednisone, required fewer than 6 months of this treatment. Of 11 patients who proceeded with second-line therapy within the first 2 years, 4 attained platelet counts above 30.0×10^9/L while maintained on drugs. Eight of 23 patients who presented with moderate thrombocytopenia attained a complete response within 2 years, and 15 patients had stable disease. None of the patients with moderate thrombocytopenia at presentation deteriorated to severe thrombocytopenia or experienced bleeding complications during follow-up.

From 86 patients with a complete response at 2 years, 9 had one or more, usually short-lived, relapses in the ensuing years. Three of the patients who relapsed had only been treated with prednisone. "Late" splenectomy induced a partial or complete response, which was sustained during follow-up, in all 3. Only 1 patient required second-line maintenance therapy to keep thrombocytes above 30.0×10^9/L. From 23 patients with a moderate thrombocytopenia at 2 years (partial response), a complete response developed spontaneously in 8 and after splenectomy in 1 during long-term follow-up. Of 8 patients with a response on maintenance therapy at 2 years, therapy was ultimately discontinued in 5, resulting in partial or complete responses in 4 within 1 year. Of 11 nonresponding patients, 1 patient ultimately responded to maintenance therapy, and 4 patients developed a partial or complete response during long-term follow-up. Therapy was discontinued and reserved for serious bleeding in the remaining patients, 4 of whom never responded. The other 2 patients obtained a complete response spontaneously after more than 1.5 years.

During the complete follow-up, 14 patients received second-line therapies, 5 of whom developed a complete or partial response.

Morbidity of patients with ITP

Table 3 shows the number of hospital admissions of patients with ITP who had survived the first 2 years after diagnosis. On average, patients had one disease-related admission in the first 2 years. Medical or surgical treatment of symptomatic thrombocytopenia underlaid 80% of these admissions.

Table 4 shows hospital admissions during long-term follow up according to the hematologic response at 2 years. As expected, patients without response or with a response on maintenance therapy had greater morbidity than the other patients. This is illustrated by high incidences of both ITP- and non-ITP–related hospital admissions.

A total of 78 patients with ITP underwent splenectomy, and this intervention was performed in 71 within 2 years after diagnosis. One patient, who died postoperatively from cytomegalovirus infection, was described earlier. Twenty other patients (26%) experienced early postoperative complications resulting in prolonged hospitalization or readmissions, and 4 patients (5%) had late complications. Observed complications were pulmonary embolism (2), intra-abdominal bleeding requiring

Table 2. Response to therapy in 152 patients presenting with thrombocytopenia, analyzed 2 years after diagnosis, stratified for platelet counts at presentation

	Severe thrombocytopenia (n = 124)							Moderate thrombocytopenia (n = 28)		
Response	CR	PR	MTR	NR	Dead	Secondary IT*	Lost to follow-up	CR	PR†	Secondary IT*
Therapy										
First-line therapy										
Prednisone	31	3	—	2	2	1	2	1	5	—
Prednisone + splenectomy	46	4	—	1	1	5	—	2	1	2
Second-line therapy‡	—	—	4	7	—	1	—	—	—	1
Other therapy§	5	2	4	2	1	—	—	1	—	2
No therapy	—	—	—	—	—	—	—	4	9	—
All, no. (%)	82 (54)	9 (6)	8 (5)	12 (8)	4 (3)	7 (5)	2 (1)	8 (5)	15 (10)	5 (3)

CR indicates complete response; PR, partial response; MTR, response to maintenance therapy; NR, no response.

*Twelve patients were reclassified as having secondary immune thrombocytopenia because they developed an autoimmune disease or malignancy during the first 2 years after the start of thrombocytopenia.

†PR at 2 years in patients with moderate thrombocytopenia denotes stable disease.

‡After failure of first-line therapy.

§Described in "Patients and methods." Splenectomy ultimately resulted in 3 complete and 2 partial responses.

Table 3. Hospital admissions in patients with ITP during the first 2 years after initial diagnosis

	Severe thrombocytopenia (n = 111)	Moderate thrombocytopenia (n = 23)
All admissions	136	8
All ITP-related admissions	116	7
Treatment of thrombocytopenia	94	4
Splenectomy	66	4
Other treatment*	28	—
Infectious disease	7	1
Other complications of treatment†	9	—
Preparation for surgery‡	1	1
Delivery	5	1
Unrelated admissions	20	1

Admissions at initial diagnosis were excluded.

*Treatment for severe symptomatic thrombocytopenia other than splenectomy.

†Renal artery obstruction during "rebound" thrombocytosis after splenectomy, abdominal wall herniation reconstruction surgery (6), and vertebral fracture during prednisone therapy (2).

‡Strategies aimed at augmenting platelets before surgical interventions other than splenectomy.

relaparotomy (5) or transfusion (4), abdominal abscess requiring relaparotomy (2) or drainage procedures (3), abdominal wall hematoma or abscess (5), gram-negative sepsis (1), pneumonia (2), anaphylactic shock (1), hemolysis due to a transfusion reaction (1), peroneal nerve palsy (1), intestinal obstruction due to adhesions (1), reconstructive surgery of abdominal wall herniation (7), viral (transfusion) hepatitis (2), and 3 episodes of pneumococcal sepsis in one patient. Finally, 1 patient, described in detail in the following paragraph, died due to pneumococcal sepsis.

Mortality of the patient series

Table 5 shows mortality risks of patients with thrombocytopenia in relation to the general population. Mortality risks are shown depending on presenting symptoms, the response to therapy 2 years after diagnosis, and type of referral.

Compared with mortality in the general population, the mortality risk for patients with an initial diagnosis of ITP was 1.5 (95% CI, 1.1-2.2). When patients reclassified as having secondary immune thrombocytopenia during the first 2 years were excluded, the mortality risk of patients with ITP was 1.3 (95% CI, 0.89-2.0). Patients reclassified as having secondary immune thrombocytopenia within 2 years after initial diagnosis had a relative mortality risk of 6.0 (95% CI, 2.5-14.5).

When patients were studied depending on symptoms, those presenting with hemorrhagic symptoms had a similar mortality risk as patients without hemorrhagic symptoms. However, patients with ITP who 2 years after diagnosis had persistent low platelet counts below 30.0×10^9/L (no response) suffered a 4.2-fold (95% CI, 1.7-10.0) increased mortality risk. In contrast, patients with platelet count above 30.0×10^9/L on maintenance drug therapy had a mortality risk only slightly higher than the general population.

Causes of death were available from 21 patients of 24 who died during the follow-up. The 4 patients who died during the first 2 years either died due to hemorrhage (1) or infection (3). During long-term follow-up, 2 ITP-related deaths occurred, and these were both observed among patients who had not responded to therapy. Three years after ITP was diagnosed and 2.5 years after splenectomy, a 20-year-old man died of pneumococcal sepsis despite previous pneumococcal vaccination. A 35-year-old woman with a platelet count of 2.0×10^9/L (2000/μL) died of a cerebrovascular hemorrhage. Both patients had had multiple courses of different second-line therapies without favorable response. Causes of death considered unrelated to ITP consisted of cancer (4), cardiovascular disease (4), alcohol abuse (1), and dementia (2). Additionally, 4 patients had a sudden death without hemorrhagic symptoms.

Table 4. Hospital admissions during long-term follow-up of patients with ITP

	ITP-related admissions		Unrelated admissions	
	No.	Incidence per 1000 person-years	No.	Incidence per 1000 person-years
Response at 2 years				
Complete response (n = 86)	39	53	54	73
Partial response (n = 23)	5	27	30	159
Response to maintenance therapy (n = 8)	10	153	14	214
No response (n = 11)	17	183	12	129
All	71	66	110	102

Long-term follow-up started 2 years after the initial diagnosis. Data are missing for 6 of the 134 patients with ITP.

Table 5. Mortality risk of patients with thrombocytopenia, relative to the general population

Characteristics	Relative risk (95% CI)
Diagnosis	
Initial diagnosis of ITP (n = 150*)	1.5 (1.1-2.2)
ITP (n = 138)	1.3 (0.9-2.0)
Reclassified as secondary TP (n = 12)	6.0 (2.5-15.0)
Presenting symptoms	
Severe thrombocytopenia (n = 122)	1.5 (1.0-2.2)
Moderate thrombocytopenia (n = 28)	1.9 (0.8-4.5)
Hemorrhagic symptoms (n = 128)	1.5 (1.1-2.2)
No hemorrhagic symptoms (n = 22)	1.7 (0.4-6.8)
ITP depending on response to therapy†	
Complete response (n = 90)	0.7 (0.4-1.3)
Partial response (n = 24)	1.8 (0.6-5.5)
Response to maintenance therapy (n = 8)	1.8 (0.6-5.5)
No response (n = 12)	4.2 (1.7-10.0)
Referral	
Primary (n = 73)	1.9 (1.1-3.0)
Secondary (n = 77)	1.3 (0.7-2.2)

Mortality risks were estimated using the mortality rate ratio standardized for age, sex, and calendar time.

*Two patients were lost to follow-up.

†Response to therapy after 2 years of follow-up.

Discussion

We studied a large cohort of adult patients with ITP with a long and virtually complete follow-up. The results show that most patients attained a partial or complete response, with platelet levels above 30.0×10^9/L within 2 years after diagnosis while at that time all therapies had been discontinued. For 85% of patients with a definite diagnosis of ITP (75% for those who present with ITP), the disease has a benign clinical course with infrequent hospital admissions and no excess mortality compared with the general population. We observed late relapses in 10% of patients who initially had a complete response, but these relapses seldom presented medical or treatment problems. The true frequency of relapses could be higher, because we did not perform systematic observations of platelet counts. However, asymptomatic episodes of mild thrombocytopenia do not represent or cause clinically important morbidity or mortality.

Remarkably, none of the patients with moderate thrombocytopenia at presentation and during the first 3 months thereafter deteriorated to having severe thrombocytopenia or experienced bleeding complications during follow-up. The obvious absence of disease-induced morbidity, together with the observation that the treatment of ITP carries the risk of serious complications, supports the recent clinical practice to refrain from medically or surgically treating patients with moderate thrombocytopenia.

In our series, 8% of patients, all with severe thrombocytopenia at presentation, did not respond to therapy within a 2-year period. These patients, with platelet counts persistently below 30.0×10^9/L, had a 4-fold increased mortality compared with the general population and a 4-fold increased morbidity compared with other patients. Bleeding and infection equally contributed to the causes of death of these patients, who were often treated with numerous regimens of immunosuppressive therapies after corticosteroids and splenectomy had failed to induce a response.

The 5% of patients who 2 years after diagnosis were still using drug therapy to keep platelet counts above 30.0×10^9/L had only a slightly elevated mortality risk compared with the general population. It is assumed that the survival benefit of this group, as compared with the nonresponders, is due to the elevation of platelet numbers to safe levels. However, follow-up was characterized by 5 times as many ITP-related hospital admissions compared with patients with moderate thrombocytopenia who were not using medical therapy at 2 years. Therefore, morbidity was not likely to be due to reduced platelet counts but related to side effects of numerous consecutive regimens of corticosteroids and immunosuppressive drugs prescribed after first-line treatment had failed to induce a sustained response. Stasi and Pizzuto have given detailed descriptions of similar adverse events that were observed in almost 50% of second-line treatments in ITP.[7,10] Therefore, until a randomized study addresses the possible benefits of second-line therapy in a nonselected group of patients with refractory disease, the risk of hemorrhage and the risk of serious side effects of treatment remain to be carefully weighed.

Previous studies have mainly addressed hemorrhagic deaths during follow-up of patients with ITP.[1,7,11,12] In a recent analysis that pooled information from 17 case series, the rate of fatal hemorrhage was estimated at between 0.0162 and 0.0389 cases per patient-year at risk, where time at risk was defined as time with fewer than 30.0×10^9/L platelets.[16] In accordance, applying the same method to our data yielded a rate of 0.019 (results not shown). However, it has to be determined whether the relatively toxic treatment of ITP has additional adverse effects on survival. For example, corticosteroids as well as immunosuppressive drugs and the splenectomized state can induce susceptibility to severe infections. In our cohort, more patients died due to infection than due to bleeding, and the lethal infections were probably related to treatment in at least half of the cases. These deaths were generally not included in previous studies. Therefore, the only reliable estimate of the risk of dying from ITP is obtained by comparing the mortality risks of patients with those of the general population, a method we applied in the present analysis.

This case series can be assumed representative of the patient population with ITP at large, considering the lack of selection and the completeness of follow-up. This is supported by Frederiksen and Schmidt, who studied the incidence of ITP in Danish adults.[17] They searched hospital databases and additionally made a special effort to include asymptomatic patients in their cohort by interviewing primary care physicians. Similar to our results, 21% of their population consisted of asymptomatic patients.

The absence of selection of either chronic or more severe cases may be an important reason for the low percentage of patients with refractory disease in our cohort, as compared with the 35% described in most review articles.[18] In our cohort, only 11% of patients with severe thrombocytopenia ultimately proceeded to second-line therapies and, whereas 2 years after diagnosis 85% of patients had attained a platelet count above 30.0×10^9/L after cessation of therapy, after a mean follow-up of 10 years even 91% had done so. Another factor that might contribute to the discrepancy with other studies is the long follow-up that increased the chance to observe late responses. In line, in 10 of 15 patients with treatment failure, Picozzi demonstrated spontaneous normalization of platelet counts after an average of 7.5 years.[2]

In our cohort, 25% of patients had a complete response to prednisone 2 years after diagnosis. The literature contains an unexplained, extreme variation of 3% to 50% in reported remission rates on glucocorticoids.[13] The length of follow-up of the different studies, the inclusion criteria, and the definitions of response are among the possible reasons for this variation. The high response rate in our series might be due to the previously mentioned absence of selection toward severe cases of ITP.

Splenectomy clearly was the most effective treatment and contributed to half of the responses observed in our cohort. At 2 years, 75% of patients who were splenectomized had reached a partial or complete response. Relapses during long-term follow-up ultimately resulted in a success rate after splenectomy of 66%. This is in accordance with the literature; most studies suggest that approximately two-thirds of patients achieve and sustain a normal platelet count after splenectomy and require no further therapy.[13] Several recent studies have compared open with laparoscopic splenectomy for ITP.[19-25] Together these series describe 169 patients who underwent open splenectomy. The early postoperative complication rate was estimated to be 22%. In our cohort, splenectomy resulted twice in death and was accompanied in 26% of patients by early postoperative complications and in 5% by late complications. In our study, complications were twice as frequent among patients older than 65 years. Two previous case series have addressed the increased disease- and treatment-related risks for older patients.[8,26] Fulminant pneumococcal sepsis is a hazardous splenectomy-related cause of death and is not entirely prevented by vaccination. We observed this infection in 2 patients, 1 of whom died. Similarly, pneumococcal sepsis occurred in 2 of 133 splenectomized adults during an average follow-up of 8 years.[27]

Twelve (8%) patients were reclassified as having secondary immune thrombocytopenia. Although they presented with an isolated thrombocytopenia, within 2 years of diagnosis a malignancy or a systemic autoimmune disease was diagnosed. They had no distinguishing features at presentation, although moderate thrombocytopenia was more common than among other patients. The 6-fold increased mortality risk during follow-up reflects the grim outcome of the underlying diseases in this group of patients.

In conclusion, most adult patients with ITP have a good outcome with infrequent hospital admissions and no excess mortality compared with the general population. However, patients with persistent severe thrombocytopenia not responding to therapy within the first 2 years have considerable morbidity and mortality.

Acknowledgments

We thank Dr Hester van Boven and Alexander Sramek for their assistance and Dr Renee Barge and Dr Jan Cornelissen for critical reading and helpful comments.

References

1. JiJi RM, Firozvi T, Spurling CL. Chronic idiopathic thrombocytopenic purpura. Arch Intern Med. 1973;132:380-383.
2. Picozzi VJ, Roeske WR, Creger WP. Fate of therapy failures in adult idiopathic thrombocytopenic purpura. Am J Med. 1980;69:690-694.
3. Ikkala E, Kivilaakso M, Kotilainen M, Hastbacka J. Treatment of idiopathic thrombocytopenic purpura in adults. Ann Clin Res. 1978;10:83-86.
4. DiFino SM, Lachant NA, Kirshner JJ, Gottlieb AJ. Adult idiopathic thrombocytopenic purpura. Am J Med. 1980;69:430-442.
5. Jacobs P, Wood L, Dent DM. Results of treatment in immune thrombocytopenia. Q J Med. 1986; 226:153-165.
6. den Ottolander GJ, Gratama JW, de Koning J, Brand A. Long-term follow-up study of 168 patients with immune thrombocytopenia. Scand J Haematol. 1984;32:101-110.
7. 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.
8. Cortelazzo S, Finazzi G, Buelli M, Molteni A, Viero P, Barbui T. High risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenic purpura. Blood. 1991;77:31-33.
9. Schiavotto C, Rodeghiero F. Twenty years experience with treatment of idiopathic thrombocytopenic purpura in a single department: results in 490 cases. Haematologica. 1993;78(6 suppl 2):22-28.
10. Stasi R, Stipa E, Masi M, et al. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. Am J Med. 1995;98:436-442.
11. Doan C, Bouroncle BA, Wiseman BK. Idiopathic and secondary thrombocytopenic purpura: clinical study and evaluation of 381 cases over a period of 28 years. Ann Intern Med. 1960;53:861-876.
12. Linares M, Cervero A, Colomina P, et al. Chronic idiopathic thrombocytopenic purpura in the elderly. Acta Haematol. 1995;93:80-82.
13. 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.
14. The American Society of Hematology ITP practice guideline panel: Diagnosis and treatment of idiopathic thrombocytopenic purpura: recommendations of the American Society of Hematology. Ann Intern Med. 1997;126:319-326.
15. McMillan R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. Ann Intern Med. 1997;126:307-314.
16. Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. Arch Intern Med. 2000;160:1630-1638.
17. Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. Blood. 1999;94:909-913.
18. George JN, El-Harake MA, Raskob GE. Chronic idiopathic thrombocytopenic purpura. N Engl J Med. 1994;331:1207-1211.
19. Marassi A, Vignali A, Zuliani W, et al. Splenectomy for idiopathic thrombocytopenic purpura. Surg Endosc. 1999;13:17-20.
20. Lozano-Salazar RR, Herrera MF, Vargas-Vorackova F, Lopez-Karpovitch X. Laparoscopic versus open splenectomy for immune thrombocytopenic purpura. Am J Surg. 1998;176:366-369.
21. Shimomatsuya T, Horiuchi T. Laparoscopic splenectomy for treatment of patients with idiopathic thrombocytopenic purpura. Surg Endosc. 1999; 13:563-566.
22. Delaitre B, Pitre J. Laparoscopic splenectomy versus open splenectomy: a comparative study. Hepatogastroenterology. 1997;44:45-49.
23. Friedman RL, Fallas MJ, Carroll BJ, Hiatt JR, Phillips EH. Laparoscopic splenectomy for ITP. Surg Endosc. 1996;10:991-995.
24. Watson DI, Coventry BJ, Chin T, Gill PG, Malycha P. Laparoscopic versus open splenectomy for immune thrombocytopenic purpura. Surgery. 1997;121:18-22.
25. Schlinkert RT, Mann D. Laparoscopic splenectomy offers advantages in selected patients with immune thrombocytopenic purpura. Am J Surg. 1995;170:624-627.
26. Guthrie TH, Brannan DP, Prisant LM. Idiopathic thrombocytopenic purpura in the older adult patient. Am J Med Sci. 1988;296:17-21.
27. Rodeghiero F, Frezzato M, Schiavotto C, Castaman G, Dini E. Fulminant sepsis in adults splenectomized for idiopathic thrombocytopenic purpura. Haematologica. 1992;77:253-256.

2001 97: 2549-2554
doi:10.1182/blood.V97.9.2549

Morbidity and mortality in adults with idiopathic thrombocytopenic purpura

Johanna E. A. Portielje, Rudi G. J. Westendorp, Hanneke C. Kluin-Nelemans and Anneke Brand

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.