Chronic immune thrombocytopenic purpura-who needs medication?

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Ann Hematol (2010) 89 (Suppl 1):S61–S65
DOI 10.1007/s00277-010-0918-0

CHRONIC ITP

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Received: 29 July 2009 / Accepted: 1 February 2010 / Published online: 23 March 2010

Abstract Chronic ITP (immune thrombocytopenic purpura; now defined as duration of more than 12 months) is not always associated with significant bleeding problems so that most children and adults can be managed expectantly with no medication unless surgery, accidents or other pathology mandate it. A cut-off platelet count of 30×10^9/l divides a group with no increased mortality from those whose risk is greater and in whom medication is usually appropriate. There is increasing recognition of long-term morbidity and mortality associated with immune suppression induced by medication and more recently new concerns have arisen about the long-term vascular complications of splenectomy. A more conservative approach to medication is warranted in many patients with chronic ITP.

Keywords Chronic ITP · Immune thrombocytopenia · Immune modulation · Splenectomy

Introduction

Immune thrombocytopenic purpura (ITP) is rarely associated with severe bleeding complications. In both paediatric and adult practice, treatment has been given to raise the platelet count on the basis that this is a surrogate indicator of bleeding risk. However, it has been demonstrated in several paediatric studies that the risk of serious bleeding is low, about 3%, and the risk of fatal bleeding, particularly from intracranial haemorrhage (ICH), very low indeed [1, 2] although this does tend to occur at the lowest counts. In the group of children who do not remit and who have chronic ITP, now defined as a duration of more than 12 months [3], many settle out with an acceptable platelet count of more than 30×10^9/l, and need no treatment unless for surgery or accidents. This is increasingly reflected in guidelines for the management of ITP [4]. Can these observations be extended to adults with ITP? There is, however, one interesting caveat—that early and intensive treatment of acute ITP may result in a reduction in the number of children and adults who develop chronic ITP. There are two lines of evidence. Firstly, recent analysis of the Intercontinental Registry Data suggests that children initially treated with IVIG were more likely to have a normal platelet count at 6 months from diagnosis than those not receiving it [5]. Secondly, the use of pulses of high-dose dexamethasone in two pilot studies in adults [6] (40 mg daily for 4 days every 14 or 28 days for four to six cycles) suggest a higher rate and a longer duration of remission, and this is now being tested in a prospective randomised study. If these results are confirmed, there will be a stronger case for medication at presentation.

In recent years, there has been an increasing recognition of two factors, firstly that the incidence of serious bleeding is also low in adults, and secondly, long-term treatment with immunosuppressive agents is associated with an increased morbidity and mortality from infection. In addition, although a systematic review of splenectomy suggested that is still the most reliable treatment in terms of remission induction [7], there is increasing evidence of long-term morbidity from vascular events [8]. In addition, a more recent review of 185 patients undergoing splenectomy demonstrated that 51% required additional therapy within a year; at 5 years, only 27% still had a response to splenectomy, and at 10 years this had fallen to 18% [9].

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Literature review: outcome of patients with chronic ITP

A retrospective analysis was reported of 310 patients with ITP seen in a single centre in Italy [10], whose age at diagnosis ranged from 8–87 years (median 40). Eighteen were diagnosed in childhood, i.e. less than16 years of age. Patients who had symptoms of bleeding at diagnosis were more likely to have bleeding later during follow-up. There was only one death, from intracranial haemorrhage in a 43-year-old woman who had persistent severe bleeding symptoms and was refractory to treatment. There are no comments on whether there were any other deaths from other causes, in particular, infection.

Another retrospective follow-up study was performed of 152 consecutive patients with ITP seen in a single centre (Leiden) [11], all older than 15 years at diagnosis and treated in a standardised manner. Four patients with severe thrombocytopenia died within the first 2 years of follow-up; one from bleeding (a 40-year-old woman from ICH with a count of 3×10^9/l), and three in relation to infection (an 86-year-old woman with a count of 63×10^9/l died from severe infection after a 3-month treatment with steroids and immune suppression; a 65-year-old woman died with normal count from sepsis after steroids for 3 months; and an 83-year-old man died after splenectomy complicated by a myocardial infarction, with a normal platelet count, from pneumonia caused by cytomegalovirus).

During long-term follow-up of these patients, two further deaths occurred related to ITP; a 20-year-old man from pneumococcal sepsis 2.5 years post-splenectomy, and a 35-year-old woman from ICH when her count was 2×10^9/l. This review indicates that people whose platelet count is persistently $<30\times10^9$/l AND who are refractory to treatment, have an increased mortality risk relative to the general population of 4.2 (CI 1.7–10). Patients who were on continuing treatment and maintaining platelet counts above this level did not have an increased risk. Complete responders have no increased mortality risk. Additionally, patients who had secondary ITP, i.e. had another disease associated with ITP such as rheumatoid arthritis, SLE or other autoimmune disease (12 patients) also had an increased mortality ratio of 6.0 (CI 2.5–15). This review is the foundation for using 30×10^9/l as a 'safe' cut-off for platelet counts, and is justification for not using medication to raise the count unless there are other considerations, such as other pathology likely to increase the bleeding risk, surgery or injury.

Seventeen case series with 1,817 patients were pooled to estimate the mortality risk from ITP [12]. There were 49 cases of fatal haemorrhage over 1,258–3,023 patient-years at risk, giving an estimated rate of fatal bleeding of 0.0162 to 0.0389 cases per patient-year at risk (when the count was $<30\times10^9$/l). Various predictions are made on the basis of this, so a 30-year-old woman remaining thrombocytopenic was predicted to lose 20.4 years of her potential life-expectancy. The data is reconsidered in the light of the Leiden data [11] to a lower risk, a loss of 10.43 years of life due to bleeding risk.

The outcome of 183 patients aged 4–75 years of age who had chronic ITP and who were treated by splenectomy [13] was studied. Forty seven (26%) were considered refractory (including seven children) with a platelet count of <100. Patients diagnosed between January 1985 and December 1994 were followed for 5 to 15 years, comprising 158 adults and 25 children, aged 15 years or younger. Several of the 47 achieved adequate counts, 12 needed no treatment and a further 27/35 responded leaving only eight, of whom five had platelet count <20 without any response to treatment (up to six different attempts). Three of these died from bleeding, two from ICH and one from massive gastrointestinal haemorrhage. So, the mortality was 6% of refractory patients, but overall 1.6% of those who had splenectomy.

Long-term follow-up of an unselected UK cohort of 245 cases presenting with ITP between January 1993 and December 1999 reports that 30 (12%) presented with bleeding [14]. Interestingly, the majority achieved remission (155/245—63%) and a further 59 had counts $>30\times10^9$/l. There was one acute death from gastrointestinal bleeding on day 5, and one death from sepsis 15 days after splenectomy. Only 30 (12%) patients proceeded to splenectomy, seven did not remit but remained asymptomatic.

A further review of adults with chronic ITP also concludes that adults may have a better prognosis than previously thought [15].

Local review of practice

We undertook a retrospective review in 2006 of cases of ITP presenting to our institution between 1/1/1996 and 31/12/2005. One objective of this was to compare practice between the consultant haematologists, and to see if there was any evidence of a change in management over time, particularly as a result of the publication of UK guidelines [16].

Cases were identified by the WHO coding D69.3 (ITP) and from departmental records using the term 'thrombocytopenia'. Eighty-four cases were identified but 18 were excluded because they had alternative platelet-related diagnoses, mismatched case numbers or no record of ITP in the notes. The notes of the remaining 66 patients (34 male and 32 female) with ITP were reviewed. Their management was assessed against standards published in UK national guidelines in 2003 [16]. Patients were classified in this audit by the bleeding score used previously in children [17]. Irrespective of the platelet count, the bleeding symptoms at presentation were

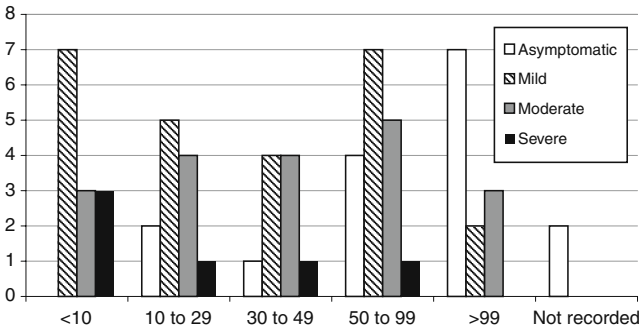

Fig. 1 Platelet count ($\times 10^9$/l) at presentation and the relationship to the classification of ITP by bleeding symptoms

classified by the auditor on the basis of the observations recorded in the case notes as 'asymptomatic', 'mild', 'moderate' or 'severe'.

Twenty five of 66 had a platelet count $<30\times10^9$/l at presentation and all but one of these received treatment to raise the count. Interestingly and perhaps surprisingly, 32/39 (59%) of those with a count above 30 received treatment. In this sequential unselected group of people, it was notable that only 9% (6/66) presented with severe bleeding requiring emergency treatment. Half of these (3) had counts $>10\times10^9$/l and presented with menorrhagia, haematuria and haematemesis. Seven of 13 patients with counts $<10\times10^9$/l had mild symptoms only. The relationship between the bleeding score and the platelet count is shown in Fig. 1. This shows that in adults, as in children, most people with very low counts ($<20\times10^9$/l) have mild symptoms or are asymptomatic. Severe bleeding was not only seen in patients with very low counts and is likely due to the fact that adults, compared to children, are likely to have co-morbid conditions which increase vulnerability to bleeding with thrombocytopenia. There were no deaths directly related to ITP in this series; one man died from pneumonia.

Splenectomy was performed in 11 cases, the majority, nine, before 2004. A higher proportion of these relapsed (5/11) than generally reported in the literature. This may represent patient selection since an analysis of several reported series has demonstrated that splenectomy is still the best long-term treatment for ITP [7] with a remission rate of 66% in 2,623 patients (apart from possibly the new thrombopoietin mimetic agents where response rates approach 70–80% [18, 19]).

A significant number of patients in our series (17/66—26%) entered a complete remission with (14) or without (3) treatment. Many patients have now defaulted from regular follow-up despite evidence of chronic ITP, leaving 16 of 37

Table 1 Case studies illustrating the difficulties with current management of chronic ITP in adults

Case 1	A 40-year-old teacher went to her doctor with fatigue. A full blood count was normal apart from a platelet count of 37×10^9/l. She was followed-up without bleeding symptoms for 3 years when her count fell to 12, still without symptoms apart from heavier periods. She was started on high-dose steroids with a good response but unacceptable side effects ('a wallop to my system', weight gain of 4 kg, being edgy and tired at work, sleeplessness). She was very upset that the next treatment offered was splenectomy, and was referred for a further opinion. She has been well on no treatment for a further 2 years, before her count dipped to less than 20. Alternative treatments are being explored
Case 2	A 57-year-old IT manager with a past history of thyrotoxicosis and severe thyroid eye disease developed sudden onset of purpura, mucosal bleeding and epistaxis a few days after a flu-like illness. He had suffered a myocardial infarction 12 weeks before, and weighed 130 kg. He did not respond to massive doses of steroid (equivalent to more than 400 mg of prednisolone daily) nor to IVIG 1 g/kg. Hepatitis screening 1 week after IVIG demonstrated HBV core antibodies at high titre suggesting previous infection and negating rituximab (but in fact, this was likely to have been from the IVIG as these antibodies were absent when tested again 2 months later). He received ciclosporin and responded with a platelet count rising to $50–60\times10^9$/l which permitted coronary angiography followed by coronary angioplasty and stenting for his narrowed left anterior descending artery. He was anxious to stop the ciclosporin because of nausea but this was not advisable during the necessary coronary interventions
Case 3	A 77-year-old retired dentist developed ITP 20 years ago. He received steroids for 18 months and remitted until 2006 since when he has required variable doses of steroids to keep his count $>30\times10^9$/l. He had a splenectomy in 2007 but relapsed shortly afterwards. He had unacceptable side effects from Dapsone (anaemia and feeling unwell) and from ciclosporin (hypertension and a macular branch vein occlusion related to this). He now has ruptured ligaments in his right ankle possibly precipitated by long-term steroid therapy. The ciclosporin resulted in a stable platelet count above 30×10^9/l
Case 4	A 29-year-old woman was diagnosed with ITP aged 11; she had splenectomy aged 14, is haemorrhagic when platelets are low and has failed therapy with high-dose dexamethasone, ciclosporin, danazol, rituximab and mycophenolate mofetil. She has bone pain from osteoporosis related to the steroids and requires high-dose steroids to control her haemorrhagic symptoms which occur when her count drops below 20×10^9/l. She has been unable to work for 5 years
Case 5	A 62-year-old printer developed ITP aged 5 years, and had a splenectomy at about that age. In 1977, he was symptomatic and was treated with high-dose steroids to no effect. In 1986, aged 38, he presented with headache caused by a subarachnoid haemorrhage (SAH) managed with combination therapy to some effect (high-dose dexamethsone, danazol and vincristine) and surgery. He was maintained on steroids but failed ciclosporin, azathioprine and danazol and tailed off his steroids 3 years after his SAH because of side effects. Since then, i.e. for the past 20 years, he has been on no therapy with a count always less than 10 but no symptoms. He declined rituximab as he felt better with no toxic therapy. However, recently, he has had a work-related hand injury and now requires joint replacement surgery to correct the resulting deformity

still under long-term review, although some of these are only seen annually.

Generally, the management of this patient group was in keeping with the UK guidelines, using steroids or IVIG as first-line therapy, and various other second-line agents. It is interesting that some patients default from follow-up. In the current series of patients being followed-up by this author, there are four who are refractory to therapy and on no treatment, with platelet counts persistently less than 20×10^9/l and no bleeding symptoms at all. These patients (who have received up to five agents) are very wary of accepting any new treatment which may make them feel worse than the disease which causes them no trouble. Two of three have also failed a new thrombopoietic agent (Eltrombopag) and a fourth has declined to participate in a clinical trial of romiplostim as he is entirely happy with no symptoms, working full time and unworried by his very low count. Several observations suggest that doctors are not sufficiently aware of the difficult side effects experienced by patients in relation to their medication. Steroids may be effective in raising the count, but are hated by patients, and often not withdrawn in a timely manner resulting in long-term side effects and damage which can be catastrophic [20, 21]. There was a lack of documentation in the case notes of the side effects of steroids and greater attention should now given to prevention of osteoporosis by adding calcium and biphosphonates according to guidelines [22, 23].

Our consecutive series is consistent with data from the other UK study [14] suggesting that a greater number of adults with ITP remit than is generally reflected in the literature. Rituximab was used for four patients, none of whom responded. While data in the literature is encouraging, this is tempered by recent reports of PML in heavily pretreated patients, including some with ITP [24].

Case studies

The problems with current therapies can be illustrated by the case studies of current patients shown in Table 1. Many patients with chronic ITP have significant side effects from treatment and little bleeding from the low count. Other patients (such as case 2 in the table) require therapy to maintain an adequate count to permit surgery or anticoagulation.

Conclusions

Many patients with chronic ITP do not require medication to raise the platelet count. Treatment must be individualised and based on symptoms and co-morbidities in addition to the platelet count and this is reflected in the recent international consensus report on ITP [25]. The toxicity of many currently available agents is unacceptable to patients, and efficacy is very variable. Long-term follow-up of some promising treatments such as rituximab and splenectomy has demonstrated some worrying toxicities which need to be taken into account when planning treatment. The new thrombopoietin mimetic agents seem promising, but longer follow-up is required to determine safety.

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