ORIGINAL ARTICLE

Adult Idiopathic Thrombocytopenic Purpura Without the Option of Splenectomy

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Summary

In this part of Malaysia, consent for splenectomy is virtually unobtainable, so we studied the outcome of ITP without this treatment option. Thirty-two adult patients were seen, but 7 defaulted before therapy evaluation. Of the remaining 25, 17 achieved a complete remission with prednisolone, but in only 8 was this prolonged. Twelve patients, who failed to respond to prednisolone or who required >15mg/day as maintenance, were offered splenectomy, but all refused. Of these 12: one has died from an intracranial haemorrhage; three others have defaulted while on no treatment with platelet counts of $<16x10^9/l$; one has had a baby who ,died from intracranial bleeding. The other seven patients have platelet counts ranging from 4 - $202x10^9/l$ with moderate bleeding on doses of prednisolone of 0-60mg/day: long-term corticosteroid side-effects are evident in all but one of them. This study demonstrates that ITP patients who refuse splenectomy have a high morbidity.

Key Words: Immune thrombocytopenia, Therapy, Splenectomy

Introduction

In most recent series of patients with immune thrombocytopenia (ITP), about 40-65% of the patients who have either failed to respond to corticosteroid, or who have relapsed once or twice on tailing the dose, have undergone splenectomy[1,2]. Approximately 65% of patients achieve prolonged complete remissions after splenectomy, although lower remission rates are reported in patients more than 45 years old[3]. It is not since the early decades of this century that the 'natural' history of ITP, without the option of splenectomy, has been reported[4]. In that series, 52 patients were untreated, of whom 18 recovered spontaneously, 23 had a remitting and relapsing course, and 7 had severe chronic thrombocytopenia.

In this North-Eastern part of Malaysia, which is rural and very traditional, it is almost impossible to persuade patients to have a splenectomy for ITP. In fact, it is difficult to persuade them to have any operation or invasive procedure at all. We thus have the opportunity to study the outcome and therapy of ITP without the option of splenectomy. This paper describes a retrospective study of ITP cases presenting to this hospital. The therapeutic responses to prednisolone are analyzed, and the roles of azathioprine and danazol in steroid-refractory/dependent ITP are assessed. The treatment and morbidity/mortality of those who might well have undergone splenectomy in the West is highlighted.

Patients and Methods

A review was made of the case records of all 32 adult patients (12 years of age or over) who were diagnosed to have ITP between January 1984 and April 1993 at Hospital Universiti Sains Malaysia, Kelantan. The criteria used for the diagnosis of ITP were: (1) platelet count less than $100x10^9/l$; (2) normal or increased

numbers of megakaryocytes in the bone marrow; (3) exclusion of other causes of thrombocytopenia such as drug-induced, acute viral infection and clinically overt connective tissue disease; (4) absence of a grossly enlarged spleen.

Antinuclear antibody (ANA) was tested in 30 cases, and a direct Coombs' test (DCT) in 24. Concurrent haemolytic anaemia (AIHA) was said to be present if the patient had a positive DCT, a haemoglobin of less than 110g/L, a raised reticulocyte count and an unconjugated bilirubin of more than 20μmol/L.

In all cases, the initial therapy was prednisolone at a dose of 60mg/day, increased to 100mg/day after 2 weeks if there was no response. The dose of prednisolone was tailed off slowly (over about 2 - 3 months) once the platelet count had returned to normal. Danazol (200mg tds) and/or azathioprine (100mg/day) for at least 8 weeks, were tried separately in 8 patients who did not achieve complete remission with prednisolone, or who required a dose of prednisolone more than 15mg/day to maintain an acceptable platelet count. Anti-D globulin (Rhesuman, Swiss Serum and Vaccine Institute, Berne) was given intravenously at a dose of 1mg/day for 4 days to two Rhesus(D) positive patients according to the protocol of Salama *et al*[5]. Ascorbic acid 2g/day was given in 2 patients, each for 8 weeks. Intravenous immunoglobulin is not used at this hospital because of its cost.

The 32 cases were followed up for 0.25 - 111 months, but the 7 cases who were followed for less than 6 months were considered ineligible for analysis of response to therapy. The median follow-up of the remaining 25 cases is 38 months.

The therapeutic responses were classified as follows (amended from reference 1):

Prolonged Complete Remission (PCR): A platelet count of >100x10^9/l achieved during treatment and maintained (>100x10^9/l) for at least 6 months after the treatment was discontinued.

Complete Remission with Relapse (CR+RE): A platelet count of >100x10^9/l during treatment, followed by a fall below 100x10^9/l after treatment was stopped. These cases were not retreated immediately either because of patient default, or physician's impression that treatment was not necessary.

Treatment Dependent Complete Remission (TDCR): A platelet count of >100x10^9/l during treatment, followed by a fall below 100x10^9/l after treatment was reduced or stopped, requiring continued therapy to sustain an acceptable platelet count.

Partial Response (PR): Symptomatic improvement with a platelet count greater than 50x10^9/l, but less than 100, for a period lasting at least 3 months during therapy.

No Response (NR): Any response less than PR.

Fisher's exact probability test was used for statistical analyses (single-tailed P values are quoted).

Results

Thirty-two new adult cases of ITP were seen between January 1984 and April 1993. Twenty-five were female and 7 male (3.6:1). The mean age was 31.6 years (range 12-80), with 62.5% of patients being under 30, and 25% under 20. The mean platelet count at presentation was 21.3x10^9/l (range 3 - 77). The DCT was positive in 4 out of 24 cases tested, of whom 2 had evidence of AIHA (Evans' syndrome).

Three of the 30 patients tested for ANA were positive at presentation, but they were negative for double-stranded DNA antibodies. One of them was a case of Evans' syndrome, who also had proteinuria but no other evidence of systemic lupus erythematosus (SLE). Another one developed full-blown SLE with renal and cerebral involvement, after three years follow-up. The third one defaulted follow-up and treatment, but returned 5 years later with a massive intracranial haemorrhage and died: at that time her platelet count was 41x10^9/l, but there was no evidence of clinical SLE.

Therapeutic response

Response to therapy was not assessed in seven patients: two patients, with platelet counts of 50 and 69x10^9/L

respectively, were not treated at all; four patients defaulted within six months; and one has not yet been observed for six months. The responses are shown in Table I. Of the 25 evaluable patients, 17 (68%) achieved a complete remission (CR), but in only eight (32%) was this prolonged (PCR). However, four patients with a PCR did subsequently relapse, but three of these again achieved a PCR with prednisolone alone. Of the six patients (24%) who relapsed after a CR (CR+RE) three were not re-treated (two defaulted and one required no treatment as her platelet count was $90x10^9/l$). The responses did not depend on the age of the patient (CR was obtained in 12/18 aged <30, and 5/7 aged >30, p=0.61), nor on the length of symptoms prior to presentation (CR was obtained in 6/9 with less than 2 weeks of symptoms, and 11/16 with more than 2 weeks symptoms, p=0.63).

Four out of seven patients achieved a worthwhile response with danazol: one achieved a PCR and is in continuing complete remission 2 years after stopping it, having initially obtained only a PR with prednisolone; another three each achieved a worthwhile PR. Only one out of four responded (with a PR) to azathioprine.

Anti-D produced NR in both of two Rhesus (D) positive patients. Ascorbic acid produced 1 NR and 1 PR.

Final status

The final status of our 32 patients is as follows: one patient has died; 16 patients have been lost to follow-up; 15 are still on follow-up. The majority of those who are 'lost to follow-up' were already off treatment with normal platelet counts. However, two were still on treatment, and two had very low levels of platelet count but were not being treated, because of failure of satisfactory response to previous therapies: unfortunately we do not know what morbidity or mortality this group has suffered.

Twelve patients who had a poor response to prednisolone, or who required a maintenance dose greater than 15mg/day, were offered splenectomy, but all refused. Their latest status is shown in Table II.

Discussion

In general, the characteristics of our patients are similar to other published series of adult ITP[1,2]. The majority of patients were under 30 years of age (65%), and female (78%). The concurrence of ITP with AIHA (Evans' syndrome) is relatively infrequent. DiFino *et al*[2] found 11% of ITP patients had a positive DCT with 3.3% having haemolysis, but Pizzutto *et al*[1] found AIHA in only 0.8% of their patients. However,

Table I
Responses to prednisolone therapy

Initial treatment		Retreatment*
Responses	**Number (%)**	**Number**
Prolonged complete response (PCR)	8 (32%)	3 PCR, 1 PR
Complete response with relapse (CR+RE)	6 (24%)	1 PCR, 1 CR+RE, 1 TDCR, 3 not treated
Treatment-dependent complete response (TDCR)	3 (12%)	-
Partial response (PR)	3 (12%)	-
No response (NR)	5 (20%)	1 NR

*The responses of 25 ITP patients to prednisolone therapy, followed from 6-111 months. *The column headed 'Retreatment' shows the responses of patients who, having first achieved the responses shown in the first column, subsequently received a second course of prednisolone (on relapse or worsening of their condition).*

Table II
Status of 12 ITP patients who refused splenectomy

Initials	Age (years)	Sex	Follow-up (months)	Platelet count (x10⁹/L)	Drugs	Bleeding problems	Other problems
Died							
RM	24	F	59	41	Nil	Intracranial, after defaulting	Died of the intracranial haemorrhage (ANA +ve)
Defaulted follow-up							
MR	23	M	52	14	P-60	Knee haemarthrosis Bruising +/-	–
RMD	57	F	6	15	P-40, A-100	Petechiae +	Cushingoid
CH	31	F	26	7	Nil	Petechiae +, Bruising +	–
On follow-up							
MSA	30	M	74	10	Nil	Post-traumatic bleeding only	–
NR	25	F	18	9	Nil	Petechiae +/-	Delivered an affected baby who died of cerebral haemorrhage
MS	34	F	38	202	P-20	Nil	ANA positive. Also has well-controlled AIHA and mild proteinuria
MAB	29	F	42	186	P-15	–	Cushingoid +
LAH	45	F	52	172	P-60, Cyc-75	Nil	SLE with renal & cerebral disease. Cushingoid ++. Skin Candida. Hypertension on treatment
NO	36	F	83	4	P-35, D-600	Bruising +, menorrhagia and iron deficiency	Cushingoid ++
HZ	50	F	43	23	P-25, D-600	Bruising ++, menorrhagia and iron deficiency	Cushingoid ++
MO	26	F	30	42	P-10	Purpura +/-	Hypertension. Mild diabetes. Previous hirsutism and neuropathy while on danazol

The latest known status (platelet count, bleeding and other problems) and treatment of the 12 patients who were offered a splenectomy for their ITP, but refused.

Drugs = therapy at latest follow-up (P = prednisolone, A = Azathioprine, D = danazol, Cyc = cyclophosphamide, daily doses in mg). ANA = antinuclear antibody, SLE = systemic lupus erythematosus, AIHA = autoimmune haemolytic anaemia

in our series it was more common, with 4 out of 24 cases (17%) tested having a positive DCT, with evidence for haemolysis in 2, one of whom is also ANA positive. Three of 30 (10%) patients tested were ANA positive at presentation, with one developing frank SLE on follow-up so far. This is similar to other series[6].

The response to prednisolone in our patients (65% achieving a CR, 32% a PCR) is similar to that reported by others[1,2]. In fact, 4 of our 8 patients with a PCR did relapse (more than 6 months off treatment) but 3 of these 4 achieved a second PCR with prednisolone alone, and one has now had a third PCR. There was no significant relationship between response to prednisolone and the age of the patient or duration of symptoms, in contrast to other studies[1,2], but our numbers are small.

Splenectomy is accepted as the most successful therapy for patients with ITP who fail to respond completely to prednisolone: long-term responses of about 65% are reported[1,2]. As surgery is not accepted by our patients who mostly come from rural and traditional families, we have had the opportunity to study the course of ITP when splenectomy is not an option.

In our patients who failed to make or maintain a satisfactory response to prednisolone, danazol appeared more effective than azathioprine (4 out of 7, versus 1 out 4 responses). We may have given azathioprine at too low a dose for too short a time, as Quinquandon *et al*[7] achieved 50% good responses using azathioprine 150mg/day for a median of 4 months. However, our low response rate may also be because non-splenectomised patients respond less well than splenectomised ones. Overall, danazol may be the best second-line therapy in ITP[8], and obviates the need for splenectomy in some cases[9]. Ahn *et al*[10] reported a 61% response rate to danazol in ITP, although their series contained both acute and chronic cases. They stressed the need for prolonged therapy (at least 6 months) and with more prolonged therapy we might have seen a better response rate. *Anderson reports prolonged CR in 10 out of 10 heavily pretreated ITP patients who were given pulsed high-dose dexamethasone[11]. As discussed in the accompanying editorial[12], these impressive results require confirmation from other centres before this therapy becomes accepted as standard second or third line therapy, in preference to the 14 or so other currently utilized treatments for chronic ITP!*

Splenectomy was offered to 12 patients, but all refused (Table I). Of these 12, one has died of intracranial haemorrhage after defaulting follow-up, emphasizing that ITP does have a mortality. Three others have also defaulted, having platelet counts below $16x10^9/l$ when last seen (early and late default is another common feature of practice in Kelantan). Only two of the other 7 are not on treatment: one (MSA) has had little response to prednisolone or danazol and very few bleeding symptoms despite a platelet count of only $10x10^9/l$; the other (NR) has a relative lack of symptoms, a total lack of response to prednisolone and anti-D, and she is not a candidate for danazol or azathioprine because she is trying to become pregnant again after the loss of her first baby. Three others (MS, MAB, LAH) are in treatment-dependent complete remissions, one having cyclophosphamide as well because of lupus nephritis: we are slowly reducing the dose of prednisolone in these three cases. The final 3 (NO, HZ, MO) struggle on with severe thrombocytopenia, variable bleeding symptoms and many side effects, mainly due to the corticosteroid. Danazol has had the advantage of ameliorating menorrhagia as well as thrombocytopenia in two patients. We believe that splenectomy could have reduced the morbidity and mortality in these 12 patients. This study supports the current widespread recommendation that ITP patients, who fail to make a satisfactory response to corticosteroids, should undergo a splenectomy. *In Kelantan, this study provides data which can be used to convince our patients to have this operation when indicated.*

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