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Platelet kinetic study in patients with idiopathic thrombocytopenic purpura (ITP) refractory or relapsing after corticosteroid treatment

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Background: A platelet kinetic study (PKS) is not indicated in the evaluation of adult patients with idiopathic thrombocytopenic purpura (ITP) at presentation. However, in ITP patients refractory to or relapsing after corticosteroid therapy, its appropriateness is considered uncertain.
Methods: We prospectively performed a PKS with ^{111}In oxine-labeled autologous platelets in 93 consecutive adult ITP patients failing steroid treatment.
Results: In 22 patients (24%) a primary condition accounting for thrombocytopenia was identified (17 with myelodysplastic syndrome and three aplastic anemia). Non-ITP patients had significantly longer platelet circulating life span ($P=0.0001$), lower splenic platelet uptake ($P=0.008$) and higher liver platelet uptake ($P=0.05$) compared to 71 patients with confirmed ITP. Among ITP patients with platelets persistently $<50\times10^9$/L, splenectomy was considered in 48 cases. In 23 (48%) it was prospectively excluded because of platelet life span $\geqslant$ 7 days (11 cases), no splenic platelet uptake together with high liver uptake (10 cases), or both conditions (two cases). Splenectomy was successfully carried out in the other 25 patients, obtaining a response rate of 100% (22 complete responses; three partial responses). Persistent relapse occurred in six of 25 (24%) splenectomized patients after a median of three months (range 1–8). PKS parameters were not able to predict post-splenectomy relapse, although relapsed patients had lower splenic/hepatic platelet uptake ratio (2.6 in relapsed *vs* 4.9 in persistently responsive patients; $P=0.08$).
Conclusions: It was concluded that in patients with chronic ITP failing steroid therapy, some PKS parameters may be prospectively used to increase the short term success rate of splenectomy.
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Introduction

Idiopathic thrombocytopenic purpura (ITP) is a chronic acquired disease characterized by isolated thrombocytopenia as clinical presentation in the absence of other causes of thrombocytopenia.[1,2] Appropriate diagnostic and treatment strategies for ITP are still uncertain, although practice guidelines, based on the opinion of a panel of experts, were recently developed by the American Society of Hematology.[3] The role of platelet kinetic study (PKS) in the diagnostic workup of patients with thrombocytopenia is controversial. With the use of ^{111}In-labeled autologous platelets a number of studies have shown that discrimination between disorders characterized by decreased production or increased destruction of platelets can be obtained by measuring platelet survival time and platelet turnover.[4,5] Moreover, PKS proved useful in determining the site of platelet destruction and in predicting the short-term therapeutic efficacy of splenectomy in some[6–10] but not in all studies.[5,11]

According to ASH practice guideline,[3] a PKS is considered both unnecessary and inappropriate in the routine testing of every adult patient with ITP at presentation. In ITP patients who fail to respond to steroid treatment and may be considered for splenectomy, the appropriateness of a PKS is considered uncertain.

In the present study 93 consecutive adult patients with thrombocytopenia who relapsed or did not respond to initial steroid treatment were investigated with PKS as part of a second level diagnostic work-up.

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The results of PKS were used to select candidates for splenectomy and the outcome of all cases was prospectively followed.

Patients and methods

Patients

During a five-year period, 93 thrombocytopenic patients refractory or relapsing after corticosteroids consecutively underwent a PKS at our Institution.

Their characteristics were as follows: median age: 49 years (range: 3–86), male/female ratio: 31/62; median platelet level: 25×10^9/L (range: 1–76), median time from diagnosis to platelet kinetic study: four months (range: 1–231). All patients met the ASH guideline criteria for ITP diagnosis (careful history, physical examination, complete blood count, peripheral blood smear morphology and HIV testing) and did not have a sustained increase in platelet levels $> 50 \times 10^9$/L after a course of prednisone therapy at the minimum dosage of 1 mg/kg for one month. In addition to PKS, patients underwent a number of different diagnostic tests, which included bone marrow morphology in all cases, cytogenetics, a search for antinuclear and antiphospholipid antibodies, serum complement levels, coagulation studies, abdominal ultrasound and virologic studies, as clinically indicated.

Platelet kinetic study

For PKS, platelets obtained from 80 ml of autologous whole blood were labeled with ^{111}In-Oxine under sterile conditions. Labeling efficiency averaged 65% (ranging from 35 to 88%). For platelet survival study, blood samples were obtained at 30 min, two and four hours, and thereafter daily until the fifth day, after reinjection of labeled platelets. The radioactivity of platelets separated from 10 ml of whole blood samples was counted in a well scintillation counter with the pulse-height analyzer set to include the 172 and 247 KeV peaks of ^{111}In. Platelet survival was determined from the radioactivity disappearance curve following the recommendations of the International Committee for Standardization in Hematology panel.[12]

Platelet localization studies

Serial abdominal imaging was performed at 15, 30, 60, 120 and 240 min, one, two, three and four days after reinjection of labeled platelets using a large-field-of view gamma camera collecting both the 174 and the 247 KeV photo peaks of ^{111}In.[13] Specific organ radioactivity was obtained using visually determined regions of interest by employing a computer algorythm. It was compared to baseline values corrected for radioactive decay. The maximum increase in splenic platelet uptake (SplPUpI) and in liver platelet uptake (HepPUpI) were evaluated. Both SplPUpI and HepPUpI were expressed as a percentage of baseline values and as a score, as follows: $\leqslant$30% increase (score 0); 30 to 49% increase (score 1); 50 to 99% increase (score 2); $\geqslant$100% increase (score 3). The proportion between SplPUpI and HepPUpI (SplPUpI/HepPUpI ratio) was also analysed.

Statistical analyses

Statistical analyses were performed using paired Student's *t*-test and Fishers' exact test where appropriate.

Results

Diagnosis

A primary condition accounting for thrombocytopenia was identified in 22 of 93 patients (24%) who met the diagnostic criteria for ITP according to ASH practice guideline and failed corticosteroid treatment. Myelodysplastic syndrome was diagnosed in 17, aplastic anemia in three, chronic hepatitis in one and systemic lupus erythematosus in one. In Table 1, the platelet kinetic parameters of this group of patients are compared with those of 71 patients in which the diagnosis of ITP was confirmed after second level diagnostic workup. Significant differences were found in platelet circulating life span, shorter in ITP, in HepPUpI, borderline lower in ITP, and in SplPUpI, higher in ITP. However no clear cutoff could be detected in any kinetic parameters between the two groups.

The mean platelet count was significantly lower in ITP patients, whereas age did not differ between ITP and non-ITP patients.

Splenectomy

Among the group of 71 patients with confirmed ITP, eight patients were lost to follow up and three refused surgery. In 12 further patients splenectomy has been

Table 1 Comparison of platelet kinetic parameters between patients with idiopathic thrombocytopenia and secondary thrombocytopenia

	Thrombocytopenia		
	Idiopathic	*Secondary*	P
No. of patients	71	22	
Age (mean)	45.9	53.4	0.116[a]
Platelet $\times 10^9$/L (median)	24.5	34	0.031[a]
(range)	(1–76)	(13–76)	
Splenic platelet uptake			
Increase (%)	68.4	31.38	0.026[a]
Score (mean)	1.35	0.68	0.008[a]
Hepatic platelet uptake			
Increase (%)	39	50.59	0.157[a]
Score (mean)	0.83	1.27	0.051[a]
SplPUpI/HepPUpI ratio (mean)	4.2	3.1	0.084[a]
Platelet survival (days) (mean)	4.2	6.2	0.0021[a]

not performed to date because platelet levels have not been persistently $\leqslant 50 \times 10^9$/L.

Splenectomy was considered as a therapeutic option in 48 cases. The presence of either of the following two platelet kinetic parameters, platelet life span $\geqslant 7$ days, or the combination of absent SplPUpI (score 0) with high HepPUpI (score 2), was used to consider splenectomy as not indicated as second line treatment. Accordingly, splenectomy was not performed in 23 patients (48%), in 11 because of normal platelet life span, in 10 because of high hepatic platelet uptake combined with absent splenic platelet uptake, and in two because of both conditions. Based on the same parameters, 17 of 22 patients in which ITP had been excluded (77%) would have also been excluded from splenectomy.

Table 2 summarizes the characteristics of the group of patients selected for splenectomy in comparison with that of patients excluded from splenectomy. The two groups differed in their PKS parameters and in the number of platelets at follow-up.

Twenty-five patients actually underwent splenectomy. A course of high-dose intravenous immune globulins (IvIG) (2 g/kg body weight over five days) was given before splenectomy to 21 patients. An increase in platelet level to $\geqslant 50 \times 10^9$/L was obtained in 15 of 20 evaluable patients. One patient was intolerant to IvIG.

Response to splenectomy was obtained in 25 patients (100%). It was complete (platelets $\geqslant 100 \times 10^9$/L) in 23 (92%) and partial (platelet count $\geqslant 50 \times 10^9$/L) in two (8%). Thrombocytopenia (platelet count $< 50 \times 10^9$/L) recurred in nine patients (36%), a median of three months (range one to eight months) after splenectomy, but it was persistent in only 6 of them. Hence, splenectomy provided satisfactory long term control of thrombocytopenia in 77% of this selected group of patients. As it is shown in Table 3, neither the type of response to splenectomy or to IvIG, nor any of the platelet kinetic parameters considered were able to predict the occurrence of persistent relapse after splenectomy.

Table 2 Comparison of platelet kinetic parameters between spelectomized and non-splenectomized ITP patients

	Selected for splenectomy	*Excluded from splenectomy*	P
	25	23	
Age (mean)	43.4	50.6	n.s.[a]
Platelet $\times 10^9$/L at diagnosis (median)	23.9	24.7	n.s.[a]
Platelet survival (days) (mean)	3.0	6.2	<0.0001[a]
Splenic platelet uptake Increase (%)	71.6	29.9	<0.0001[a]
Hepatic platelet uptake Increase (%)	28.0	68.8	<0.0001[a]
SplPUpI/HepPUpI ratio (mean)	4.3	2.9	0.06[a]
Platelet $\times 10^9$/L at last f/up	264.4	111.1	0.0007[a]
On treatment	4	13	0.006[b]

[a]Student's *t*-test; [b]Fishers' exact test.

Table 3 Comparison of platelet kinetic parameters between ITP patients with sustained response to splenectomy or with persistent relapse

	Response to splenectomy *Sustained*	*Relapse*	P
No of patients	19	6	
Platelets $\times 10^9$/L after splenectomy (mean)	293.3	254.2	0.6[a]
Splenic platelet uptake Increase (%)	74.2	63.7	0.58[a]
Score (mean)	1.7	1.3	0.45[a]
Hepatic platelet uptake Increase (%)	27.9	28.2	0.98[a]
Score (mean)	0.5	0.6	0.88[a]
SplPUp/HepPUp ratio (mean)	4.9	2.6	0.08[a]
Platelet survival (days) (mean)	3.8	3.3	0.72[a]
Response to IvIG before splenectomy	12/15	2/5	0.13[a]

[a]Student's *t*-test.

Follow up

At last follow-up, after a median of 47 months, none of the patients undergoing splenectomy had died. Four patients were still receiving treatment (azathioprine in two, danazol in one and prednisone in one); among which one had a platelet count $30-50 \times 10^9$/L and another $< 30 \times 10^9$/L. Among the 23 ITP patients who did not undergo splenectomy, one patient died of cerebral hemorrage 40 days after diagnosis. At last follow up, 13 were receiving treatment (prednisone and danazol), six had thrombocytopenia $\leqslant 50 \times 10^9$/L and two had $< 30 \times 10^9$/L.

Discussion

According to ASH practice guideline,[3] the diagnosis of ITP in adult patients should be based principally on a careful history and physical examination, complete blood count, and examination of the peripheral blood smear. HIV testing is also needed in patients with risk factors. Marrow examination is not necessary but it is considered appropriate in patients over age 60 years and before splenectomy. The appropriateness of PKS, as well as of other tests such as antinuclear antibodies, direct antiglobulin, lupus anticoagulant/antiphospholipid antibodies, serum complement, abdominal ultrasound, chest X-ray and thyroid function, to confirm the diagnosis of ITP in patients failing primary treatment and before splenectomy, is considered uncertain.

In the present study among patients with ITP diagnosed according to ASH practice guideline but who were refractory or relapsed after corticosteroid treatment, the results of the second level diagnostic workup, including marrow analysis, led to the identification of a primary disease accounting for thrombocytopenia in 24% of cases. Patients in which a diagnosis different from ITP was made were affected predominantly by diseases causing impaired platelet

production. Myelodysplasia, a condition whose frequency increases with age, was the most common disease identified in our adult population. Although it generally involves multiple hematopoietic lineages and presents with multiple peripheral cytopenias, it has been reported that myelodysplasia may also be present in some patients with isolated thrombocytopenia without peripheral blood morphological abnormalities.[14,15] A marrow study is the most important diagnostic procedure in the identification of myelodysplasia. In the present unselected series, performing a marrow study at diagnosis would have excluded 20 patients (22%) from a diagnosis of ITP and consequently from corticosteroid therapy and from further diagnostic workup. In particular, a marrow study would have correctly diagnosed 19% of our patients aged <60 and 28% of those aged $\geqslant 60$, a cohort in which it is considered appropriate, according to ASH guideline. These figures should be considered when evaluating the need for a marrow study in every patient with idiopathic thrombocytopenia at diagnosis.

PKS parameters in non-ITP patients showed significantly longer platelet circulating life span, lower splenic platelets uptake and borderline higher hepatic uptake, compared to ITP patients. However, since no clear cutoff level could be identified, our study does not support the use of PKS as a single diagnostic test to discriminate between patients with ITP and thrombocytopenia secondary to other conditions. Nevertheless, a normal platelet life span and/or a low splenic platelet uptake should be considered suspicious and contribute to a careful search for a diagnosis different from classical ITP.

In patients with chronic ITP who fail corticosteroid therapy, splenectomy is considered the therapy of choice[16–18]. However, since it produces long term benefit in only two thirds of patients,[1,19–21] a number of variables have been evaluated as possible predictive factors of success.[6,22,23] In a recent study, the rise of the platelet count after a course of intravenous immune globulin predicted a response to splenectomy with a positive predictive value (PPV) of 90.5%.[24]

Platelet kinetic parameters have proven to correlate with the outcome of splenectomy in a number of retrospective studies. A normal life span was considered as a parameter predictive of the failure of splenectomy;[7] similarly, a PKS showing predominant or exclusive hepatic platelet uptake predicted the failure of splenectomy in 92% of patients.[6,10]

In the present study the prospective use of similar PKS parameters proved to be useful for the selection of ITP patients as candidates for splenectomy. By excluding patients with platelet survival of $\geqslant 7$ days or with the combination of a marked increase in hepatic platelet uptake and no increase in splenic platelet uptake, the response rate to splenectomy was 100%.

The predictive value of those platelet kinetic parameters on the short term efficacy of splenectomy was higher than the response to IvIG, which in our patients was 75%. Response to IvIG did not correlate with splenectomy outcome in a recent retrospective study.[23]

On the other hand, platelet kinetic parameters failed to predict the recurrence of persistent thrombocytopenia after splenectomy. Nevertheless, the frequency of splenectomy failure was low in our series, giving an overall long term success rate of 77% in patients selected according to PKS parameters. This figure may be higher than that commonly reported in most series in the literature where the success rate of the procedure varies from 50 to 70%[18,25] and the relapse rate is 10 to 20% in the first year.[8,26]

The long term prognosis of chronic ITP is not poor and the more recently reported disease-specific mortality rate is low.[1,27,28] In our series it was less than 2%, after a follow up of four years. Nevertheless, only 15% of relapsing patients after splenectomy required further treatment, whereas 37% of non splenectomized patients were on treatment at last follow up. The median platelet count was lower and the proportion of patients with significant thrombocytopenia was higher among non splenectomized patients. Accordingly, the role of splenectomy in the management of patients with ITP could be reconsidered and splenectomy may emerge also as a cost-effective long-term treatment-sparing therapy, particularly if its efficacy may be predicted with high accuracy.

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