Platelet sequestration studies predict response to splenectomy in Immune Thrombocytopenia (ITP): An Australian experience

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Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune disorder characterised by antibody-induced and T-cell mediated platelet destruction, and impaired megakaryocyte production due to thrombopoietin (TPO) deficiency.[1-4] Mucocutaneous bleeding and internal bleeding are serious complications of ITP, more likely to occur with marked thrombocytopenia (<10 x 10^9/L).[5] The incidence of ITP increases with age and more commonly affects females. It is diagnosed in 1-4 per 100,000 population annually.[6,7]

Current treatment guidelines recommend corticosteroids and intravenous immunoglobulin (IVIG) as first line therapy.[8] Splenectomy, TPO-receptor agonists (TPO-RAs) and Rituximab are listed as second line therapies followed by other immunosuppressive medications.[8] The spleen plays a critical role in the pathogenesis of ITP as the major site of anti-platelet antibody production and FC-receptor mediated platelet sequestration via the reticuloendothelial system .[9] As such, splenectomy has been deployed as a treatment for ITP over 70 years in patients failing first line therapy. However, the role of splenectomy in the contemporary management of ITP is becoming unclear; due to the lack of predictors of response, risk of post-splenectomy infection and emergence of TPO-RAs. [10, 11]

International studies have demonstrated the value of using platelet sequestration studies with radionuclide labelling of platelets to define the likelihood of response following a splenectomy.[12-15] This prompted us to introduce an ^{111}indium-labelled autologous platelet sequestration (ILAPS) study at our institution for relapsed/refractory ITP patients being considered for a splenectomy. [12-15]

Aims

To audit the use of ILAPS in an Australian setting and define its role in predicting response to splenectomy.

Methods

We performed a retrospective audit of all patients referred for an ILAPS study at Geelong Hospital over a 15-year period (2003 to 2018). All patients were referred once they required second line therapy; this was physician dependent. All patients with secondary ITP due to haematological or solid tumour malignancies were excluded. Outcome analysis following splenectomy was confined to patients with a minimum 12 months follow-up.

The primary objective of this audit was to evaluate whether ILAPS was predictive of patient's response after second line therapy, in particular splenectomy. Response outcomes were defined according to the International Working Group criteria (see footnotes for Table 2).[16]

All patient's had blood samples taken. Platelets were extracted and labelled with radioactive Indium-111, then transfused back into the patient. Serial static images of the liver and spleen were performed while concurrently measuring radioactivity levels in the blood (Figure 1). The spleen/liver uptake ratio at 0.5 hours to the time at which 80% of the labelled platelets were sequestered in both organs is defined as the "R" value demonstrated below:[14]

R > 2.0	Pure Splenic sequestration (PS)
R = 1.4-2.0	Predominantly splenic sequestration (PS)
R = 0.8-1.3	Mixed sequestration (M)
R <0.8	Pure hepatic sequestration (PH)

Figure 1. Splenic sequestration patterns in ILAPS study.

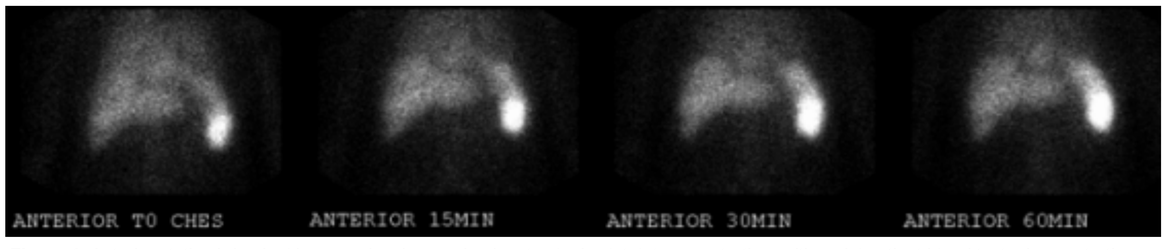

Figure 1. Anterior static abdominal images showing predominant splenic platelet sequestration, with serial patient blood tests demonstrating shortened platelet half lives consistent with platelet destruction in immune thrombocytopenia.

Results

62 patients were referred for ILAPS studies at Barwon Health (University Hospital Geelong) between 2003-2018. 45 patients were included in the final analysis; their baseline characteristics are listed below in Table 1.

Table 1. Baseline characteristics of patients

Median age at time of ILAPS (years):		38 (range 16- 82)
Gender:	***Female***	n = 24 (53.3%)
	Male	n = 21 (46.7%)
Treatment received*:*	***Splenectomy***	n = 13 (28.9%)
	Medical management	n = 32 (71.1%)
Median follow up period (months)		39.0 (range 1.0 – 157.0)
ITP type	***Primary***	n = 41 (91.1%)
	Secondary	n = 4 (8.9%)
	- *Systemic lupus erythematosus*	1
	- *Drug Induced*	2
	Flu vaccine	(1)
	Rosiglitazone	(1)
	- *Undefined bone marrow pathology*	1

Splenectomised patients were more likely to remain in complete remission (CR) compared to those conservatively managed (69.2% vs 31.3%), regardless of ILAPS. Splenectomised patients with a splenic uptake had a 100% overall response rate (ORR) with 83.3% CR and 16.7% PR rates at/beyond 12 months (Table 2). However, patients with a non-splenic uptake demonstrated a lower ORR 71.43% with 57.1% CR and 14.3% PR at/beyond 12 months. ILAPS had no influence on the outcome of patients being conservatively managed.

Table 2. Outcome of splenectomised patients post ILAPS

ILAPS sequestration pattern (n = 13)	**Pure or predominant splenic sequestration (PS) (n= 6)**	**Pure or predominant hepatic (PH) and mixed (M) sequestration (n = 7)**
Follow up period (post splenectomy) < 3 months	CR = 6	CR = 3 PR = 1 NR = 3
6-12 months	CR = 5 PR = 1	CR = 3 PR = 2 NR = 2
> 12 months	CR = 5 PR = 1	CR = 4 PR = 1 NR = 2

† Treatment outcomes post splenectomy (n = 13). Response was defined using the International Working Group criteria; Complete response (CR) - platelet count > 100 x 10^9/L; Partial response (PR) - platelet count of 30-100 x 10^9/L in the absence of bleeding; No response (NR) - platelet count < 30 x 10^9/L, steroid-dependent or platelet count < 100 with episodes of bleeding. [16]

Discussion and conclusions

The results of our audit parallel the international experience with platelet sequestration studies. Those demonstrating a splenic uptake on ILAPS are more likely to achieve and maintain CR post splenectomy. Splenectomy is an effective treatment for relapsed/ refractory chronic ITP and potentially appealing in select patients for the following reasons: greater likelihood of achieving a durable remission, declining rates of post-splenectomy infection due to prophylaxis, avoiding the need for long term medications and its adverse effects. Conversely, ILAPS also obviates the need for some patients to undergo surgery and targets those more suitable for TPO-RA's. In conclusion, our audit confirms ILAPS to be a feasible and reproducible procedure in an Australian setting and a valuable tool in predicting ITP patient's response to a splenectomy. Unfortunately, cost is the main factor limiting its' uptake in Australia.

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