

Second-Line Therapy for Immune Thrombocytopenia: Real-World Experience in Canada

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ABSTRACT

Background

The sequence of second-line therapy used for the treatment of immune thrombocytopenia (ITP) is variable. This study aimed to describe the types and sequences of second-line therapies for a large cohort of ITP patients in Canada.

Methods

We completed a retrospective cohort study of the McMaster ITP Registry. We included patients with primary or secondary ITP who had received one or more second-line therapies including any of the splenectomy, rituximab, danazol, dapson, or thrombopoietin receptor agonists (TPO-RAs), or immunosuppressant medications. Immunosuppressant medications included azathioprine, cyclophosphamide, cyclosporine, or mycophenolate given alone or in combination.

Results

We identified 204 ITP patients who had received one or more second-line therapies. The most common second-line therapies were immunosuppressant medications (n = 106; 52.0%), splenectomy (n = 106; 52.0%), TPO-RAs (n = 75; 36.8%), danazol (n = 73; 35.8%), and rituximab (n = 67; 32.8%). For patients who received only one second-line therapy (n = 88), the most common treatment was splenectomy (n = 28; 31.8%). For patients who received more than one second-line therapy (n = 116), the most common treatment sequence was splenectomy, followed by immunosuppressant medications (n = 7; 6.0%). Of the 154 evaluable patients at the end of follow-up, 69 (44.8%) achieved a complete platelet count response and 101 (65.5%) achieved a partial response.

Conclusion

Immunosuppressant medications and splenectomy are commonly used as second-line therapies for ITP in Canada. Treatment choices and the sequence of treatments were variable.

RESUME

Contexte

La séquence de la thérapie de deuxième ligne utilisée pour le traitement de la thrombocytopénie immunitaire (PTI) est variable. Cette étude visait à décrire les types et les séquences des thérapies de deuxième ligne pour une large cohorte de patients atteints de PTI au Canada.

Méthodes

Nous avons réalisé une étude de cohorte rétrospective du registre ITP de McMaster. Nous avons inclus des patients atteints de PTI primaire ou secondaire qui avaient reçu une ou plusieurs thérapies de deuxième ligne, y compris une splénectomie, du rituximab, du danazol, de la dapsone ou des agonistes des récepteurs de la thrombopoïétine (AR-TPO), ou des médicaments immunosuppresseurs. Les médicaments immunosuppresseurs comprennent l'azathioprine, le cyclophosphamide, la cyclosporine ou le mycophénolate, administrés seuls ou en combinaison.

Résultats

Nous avons identifié 204 patients atteints de PTI qui avaient reçu une ou plusieurs thérapies de seconde ligne. Les thérapies de deuxième ligne les plus courantes étaient les immunosuppresseurs (n = 106; 52.0%), la splénectomie (n = 106; 52.0%), les AR-TPO (n = 75; 36.8%), le danazol (n = 73; 35.8%) et le rituximab (n = 67; 32.8%). Pour les patients qui n'ont reçu qu'un seul traitement de deuxième intention (n = 88), le traitement le plus courant était la splénectomie (n = 28; 31.8%). Pour les patients qui ont reçu plus d'un traitement de deuxième ligne (n = 116), la séquence de traitement la plus courante *était* la splénectomie, suivie par les médicaments immunosuppresseurs (n = 7; 6.0%). Sur les 154 patients évaluables à la fin du suivi, 69 (44.8%) ont obtenu une réponse complète de la numération plaquettaire et 101 (65.5%) une réponse partielle.

Conclusion

Les médicaments immunosuppresseurs et la splénectomie sont couramment utilisés comme traitements de deuxième intention pour le PTI au Canada. Les choix de traitement et la séquence des traitements sont variables.

Keywords: immunosuppresseurs; ITP; platelets; registry; thrombocytopenia; thrombopoïétin

Introduction

Immune thrombocytopenia (ITP) is an autoimmune platelet disorder, characterized by peripheral blood platelet counts below $100 \times 10^9/L$ with no underlying cause. ITP is considered primary when there is no associated illness, and secondary when it occurs in the context of infection, malignancy, or autoimmune disease.¹ The estimated incidence of ITP is 1.6 to 3.9 per 100,000 persons per year; however, the prevalence is significantly higher, especially in adults, as the disease is often chronic and patients require multiple lines of therapy. Morbidity among patients with ITP results from bleeding,² reduced quality of life,³ fatigue,⁴ and toxicities from treatments.^{5,6}

Establishing the diagnosis of ITP can be challenging in the outpatient setting as there is no diagnostic test with adequate performance characteristics. Thus, providers must exclude other

causes of thrombocytopenia based on information they obtain from history, physical examination, and laboratory investigations. Our approach in the case of a patient with thrombocytopenia in the outpatient setting is presented in Figure 1. Once the diagnosis is established, the treatment decisions will depend on the severity of the thrombocytopenia (treatment is generally not required for platelet counts of $>30 \times 10^9/L$),^{7,8} other risk factors for bleeding (e.g., use of anticoagulant or anti-platelet medications), lifestyle activities that can be associated with trauma (e.g., high impact sports), and the presence or absence of bleeding manifestations such as petechiae and oral purpura (Figure 2).^{9,10}

First-line therapy for ITP consists of corticosteroids, with or without intravenous immune globulins or rhesus immune globulins, which are effective in raising the platelet count in

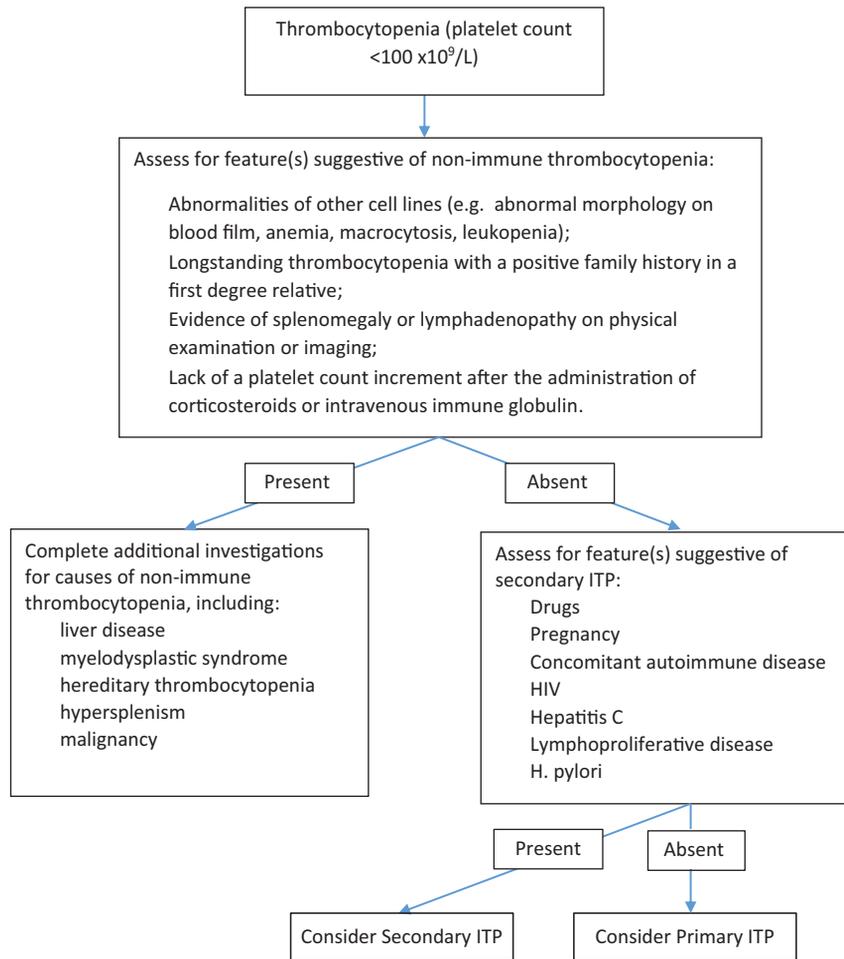


Figure 1. Diagnostic approach for the patient presenting with thrombocytopenia to the clinic as used in the McMaster Immune Thrombocytopenia (ITP) Registry.



Figure 2. Common bleeding manifestations in patients with ITP and severe thrombocytopenia include petechiae on the skin (A) and oral purpura (B).

the short term.^{1,5} For patients who relapse after corticosteroids or who are refractory to corticosteroids, second-line therapy is indicated.⁷ Treatments used for second-line therapy include splenectomy, thrombopoietin receptor agonists (TPO-RAs), rituximab, immunosuppressant medications, danazol, and dapsone. These treatments modulate the immune response by reducing antibody production, interfering with platelet destruction, or promoting platelet production.¹

Recent guidelines from the American Society of Hematology provide recommendations for the timing and sequence of second-line therapy, focusing on splenectomy, rituximab, and TPO-RAs.⁷ In addition, a recent update to the international consensus includes other treatment options, such as fostamatinib, and provides expert guidance on management.¹¹ Both reports highlight the need to individualize treatment choices based on patient factors including age, sex, comorbidities, patient preference, and access to medications.

In Canada, the choice of second-line therapy is influenced by access to medications, especially with respect to TPO-RAs and rituximab. Provincial funding for TPO-RAs through government-assisted programs is often restricted to patients having failed other second-line treatments including splenectomy.¹² Rituximab is available through private insurers or compassionate access from the manufacturer. Given these challenges, we sought to explore real-world experience with treatment choices and patterns of practices with respect to ITP treatment at a large Canadian referral center.

Methods

Study population

Patients were identified from the McMaster ITP Registry, a prospective, longitudinal registry of adult patients (≥ 18 years) that began in 2010.¹³ Consecutive patients with thrombocytopenia, those with platelet counts of $< 150 \times 10^9/L$, who were referred to the tertiary hematology clinic at McMaster University Medical Centre in Hamilton, Canada, were enrolled in the Registry. Clinical and laboratory information on diagnosis, medication use, procedures, blood counts, and bleeding events was collected prospectively every 6 months. No interventions were applied. All patients were managed by two physicians who established the diagnosis after each clinic encounter. The single-center design ensured that all patients were managed in a consistent manner. When the diagnosis was in question, it was adjudicated by chart review.¹³ We included patients with a diagnosis of primary or secondary ITP who received at least one second-line therapy and who had at least 6 months of follow-up. The follow-up ended on 30 June 2018.

The sequence of treatments administered as second-line therapy was dictated by the start date recorded in the medical

chart. To make the analysis of treatment sequences feasible, we grouped the most common immunosuppressant medications, including azathioprine, cyclophosphamide, cyclosporine, and mycophenolate, into one category. Similarly, the TPO-RA category included romiplostim and eltrombopag, both of which were available in Canada at the time of this report. All data variables were obtained from the McMaster ITP Registry including patient demographics, type of ITP treatment, treatment start dates, platelet counts, and duration of follow-up. We conducted medical chart reviews to complete missing information. After manual chart review, we found a large number of patients with missing stop dates for medications ($n = 144$). The information was unavailable because it was retrieved from limited historical data, it had not been recorded in the patient chart or registry data, or the patient was discharged from the registry. Because of this, we were unable to report the total exposure of each medication or describe the overlap with multiple medications; rather, we limited our description to the sequence of treatments based on medication start dates.

All patients were assessed for a platelet count response at the end of follow-up as a measure of treatment effectiveness. Complete response was defined as a patient platelet count of $\geq 100 \times 10^9/L$ that was maintained for at least 30 days. Partial response was a platelet count of $\geq 50 \times 10^9/L$ maintained for at least 30 days.

Statistical analysis

Patient characteristics and second-line treatments were reported descriptively. We described categorical data using counts and proportions, and continuous data using median and interquartile range (IQR).

Results

We identified 204 patients with ITP who had received at least one second-line therapy. Most patients had primary ITP ($n = 154$, 75.5%). Of the 204 patients, 117 (57.4%) were female and the overall median age at the time of registration was 54 years (IQR, 35–65). Patients had a median duration of ITP of 9 years (IQR, 4–19) from the time of initial presentation. Median duration of follow-up was 2.7 years (IQR, 0.9–5.4) (Table 1).

The median number of second-line therapies per patient was two (IQR 1–3). Overall, we identified 69 different treatment sequences. In order of frequency, treatments used as second-line therapy were immunosuppressant medications ($n = 106$, 52.0%), splenectomy ($n = 106$, 52.0%), TPO-RAs ($n = 75$, 36.8%), danazol ($n = 73$, 35.8%), and rituximab ($n = 67$, 32.8%) (Table 2). The immunosuppressant medications most commonly used were azathioprine ($n = 79$, 74.5%), followed by mycophenolate ($n = 51$, 48.1%) and cyclosporine ($n = 35$, 33.0%). For patients

Table 1. Patient Demographics

	ITP patients (N = 204)
Female (N, %)	117 (57.4%)
Age at enrollment (years) (median; Q1, Q3)	54 (35,65)
ITP Diagnosis, n (%)	
Primary ITP	154 (75.5%)
Secondary ITP	50 (24.5%)
Patients with complete record from initial presentation of ITP (N, %)	193 (94.6%)
Age at initial presentation of ITP (years) (median; Q1, Q3)	41 (25, 56)
Duration ITP (years) (median; Q1, Q3)	9 (4, 19)
Duration of follow-up (years) (median; Q1, Q3)	2.7 (0.9, 5.4)
Prevalence of second-line therapy at enrollment (N, %)	35 (17.2%)
Prevalence of second-line therapy at last follow-up (N, %)	15 (7.4%)

ITP = immune thrombocytopenia.

who received only one second-line treatment (n = 88), the most common single agents were splenectomy (n = 28, 31.8%), immunosuppressant medication (n = 21, 23.9%), or danazol (n = 18, 20.5%). Of the 116 (56.9%) patients who received more than one second-line treatment, the most common treatment sequences were splenectomy followed by immunosuppressant medication (n = 7, 6.0%); immunosuppressant medication followed by rituximab (n = 6, 5.0%); and immunosuppressant medication followed by danazol (n = 5, 4.0%) (Figure 3).

Of the 78 patients who received splenectomy in a sequence with other second-line treatments, 56 (71.8%) received splenectomy as the first therapy, 16 (20.5%) received splenectomy as the second therapy, and 6 (7.7%) received splenectomy as the third therapy in the sequence of treatments (Table 2). TPO-RAs and rituximab were more often administered later in the treatment course. Of the 64 patients who received TPO-RA as part of a sequence of treatments, 7 (10.9%) received it first, 19 (29.7%) received it second, and 38 (59.4%) received it third or later (Table 2). Similarly, of the 57 patients who received rituximab in a sequence, rituximab was administered first for 12 (21.1%) patients, second for 16 (28.1%) patients, and third or later for 29 (50.9%) patients (Table 2). The final treatment that patients received as part of a second-line therapy comprised TPO-RAs (n = 52, 25.5%), immunosuppressant medications (n = 45, 22.1%), rituximab (n = 37, 18.1%), splenectomy (n = 36, 17.6%), danazol (n = 33, 16.2%), or dapsone (n = 1, 0.5%).

We analyzed treatment responses in 154 (75.5%) patients who had platelet count measurements available at least 30 days after the last follow-up visit: 69 (44.8%) patients had a complete response, and 101 (65.6%) patients had a partial response after their last treatment.

Discussion

In this large Canadian cohort of ITP patients, we found that the most common treatments used for second-line therapy were immunosuppressant medications, splenectomy, TPO-RAs, danazol, and rituximab. Treatment sequences were variable; however, splenectomy was often received early in the course of the treatment, and TPO-RAs and rituximab were frequently received later. Our findings provide a description of ITP treatment sequences in the Canadian context, where access to certain medications is limited. The frequent use of splenectomy early in sequence may be different from other countries.¹⁴

Splenectomy has traditionally been the standard second-line therapy for adults with ITP and remains the most effective treatment, with response rates of 85% including two-thirds remaining in remission after 5–10 years.^{15–17} However, its practice has become less common in favor of other alternatives.¹⁴ Although the risk of post-splenectomy sepsis is rare, it remains a deterrent.¹⁸ More recently, TPO-RAs and rituximab have emerged as second-line ITP treatments alongside splenectomy in recent evidence-informed guidelines.⁷ Implementation of guidelines in

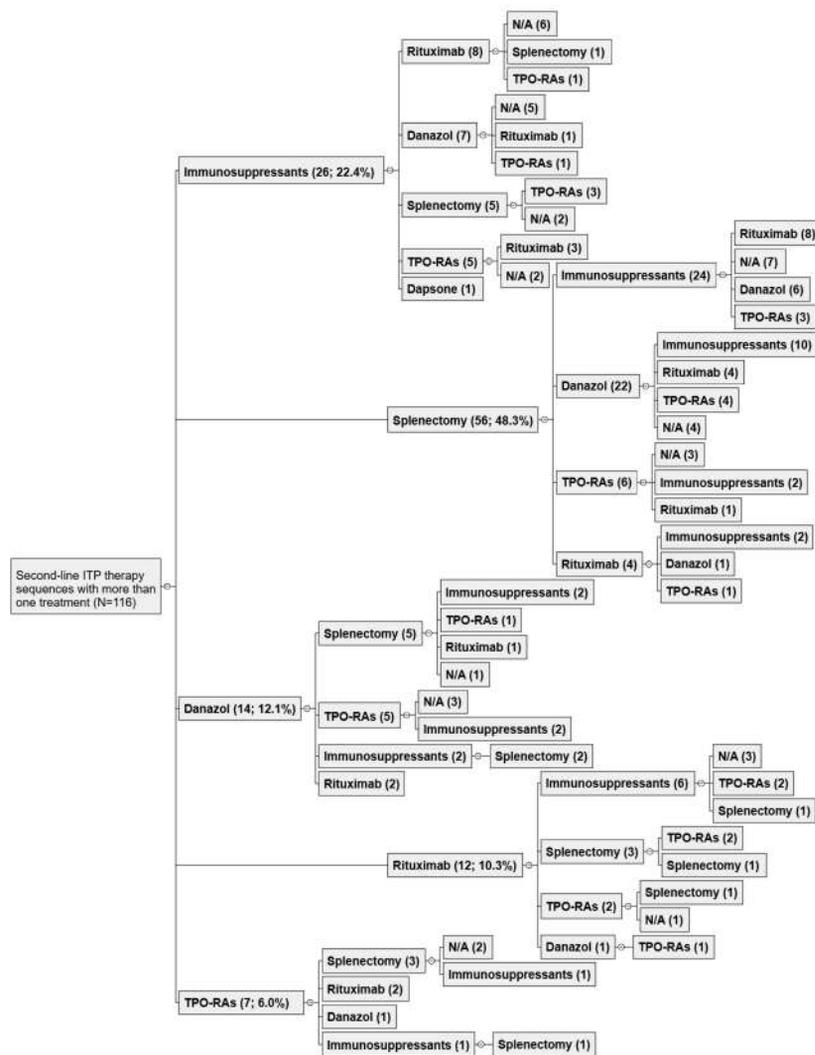


Figure 3. Order of second-line therapy received (N = 116). Each branch represents a new treatment. Shown is the sequence of treatments up to the third treatment. N/A denotes no additional treatments received.

practice will depend on some context-specific factors including patient preference and access to medications.

TPO-RAs have shown to generate platelet count responses in 59–88% of patients, whereas rituximab has been found to induce response rates ranging from 53 to 73%.^{19,20} A recent study from the Mayo Clinic found that patients who received splenectomy followed by rituximab, as opposed to rituximab followed by splenectomy, had a higher tendency to remain in remission at 2-year follow-up, suggesting that the sequence of second-line therapies may impact treatment effects.²¹ Rituximab has been associated with infusional reactions and, rarely, reactivation of latent infection.^{22,23} Eltrombopag has been associated with liver toxicity in approximately 10% of the patients, and TPO-RAs as a class have been linked to thrombotic events.²⁴ Splenectomy

and rituximab are aimed at inducing remission off therapy, while TPO-RAs are maintenance treatments.²⁴

Immunosuppressant medications, including azathioprine, cyclosporine, and mycophenolate, have been used to treat ITP for many years. Success rates with each of these agents individually range from approximately 25 to 70% at maximum efficacy,^{7,22} with some reports demonstrating improved response rates when these agents are combined.^{25,26} While immunosuppressant medications have generally been replaced by newer agents in some jurisdictions, this does not appear to be the case in Canada. To simplify the analysis, we grouped these medications together, but our findings indicate that azathioprine was most commonly used, followed by mycophenolate and cyclosporine. These agents may serve as a bridge to a more definitive treatment, as

Table 2. Second-Line Therapy for Immune Thrombocytopenia (ITP). Second-Line Therapy was Defined as Any ITP Treatment Received after First-Line Therapy, Which Includes Corticosteroids, Intravenous Immune Globulin, and Rhesus Immune Globulin

Second-line therapy	Ever received (N = 204)	Single-agent N = 88	Multiple agents N = 116	Received First	Received Second	Received third or later	Received last (N = 204)
Immunosuppressant medications*	106 (52.0%)	21 (23.9%)	85 (24.8%)	26 (30.6%)	33 (38.8%)	26 (30.6%)	45 (22.1%)
Splenectomy	106 (52.0%)	28 (31.8%)	78 (22.7%)	56 (71.8%)	16 (20.5%)	6 (7.7%)	36 (17.6%)
TPO-RA	75 (36.8%)	11 (12.5%)	64 (18.7%)	7 (10.9%)	19 (29.7%)	38 (59.4%)	52 (25.5%)
Rituximab	67 (35.8%)	10 (11.4%)	57 (16.6%)	12 (21.1%)	16 (28.1%)	29 (50.9%)	37 (22.1%)
Danazol	73 (32.8%)	18 (20.5%)	55 (16.0%)	29 (50.9%)	31 (56.4%)	10 (18.2%)	33 (16.2%)
Dapsone	4 (0.9%)	0 (0.0%)	4 (1.2%)	1 (25.0%)	1 (25.0%)	2 (50.0%)	1 (0.5%)

TPO-RA = thrombopoietin receptor agonist (eltrombopag or romiplostim).

*Includes azathioprine, cyclophosphamide, cyclosporine, or mycophenolate.

maintenance therapy in patients who achieve a platelet count response, or as a necessary treatment before becoming eligible for public funding for TPO RAs in some provinces in Canada.

Limitations of this study were the single-center design; however, this Canadian-specific context is locally informative. Missing information on the stop dates of medications did not permit an analysis of the total drug exposure duration or a description of combination therapy. Nevertheless, the data allowed for a robust description of the sequence of treatments, which was the goal of our project. Grouping of immunosuppressant medications was necessary for feasibility of the descriptive analysis; however, this strategy did not permit an evaluation of single versus combination immunosuppressant medication or drug-specific difference in treatment effects.

In conclusion, this study highlights variability in practice with respect to second-line therapy for ITP in Canada, where splenectomy and immunosuppressant medications continue to be used early in the course of treatment. Further research is needed to account for the discrepancies in practice compared with published guidelines,⁷ which favor TPO-RA, rituximab, and splenectomy as second-line treatment options, and de-emphasize immune suppressant medications.

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