ITP and international guidelines: What do we know, what do we need?

Francesco Rodeghiero, Marco Ruggeri

San Bortolo Hospital, Department of Cell Therapy and Hematology, 36100 Vicenza, Italy

Correspondence:
Francesco Rodeghiero, San Bortolo Hospital, Department of Cell Therapy and Hematology, Viale Rodolfi, 37, 36100 Vicenza, Italy.
rodeghiero@hemato.ven.it

Available online:

Summary

In the last decade, rituximab and thrombopoietin-receptor agonists (TPO-ra) have been introduced into the traditional armamentarium of Immune Thrombocytopenia (ITP), consisting in corticosteroids as initial treatment and splenectomy in those not responding or relapsing. A variety of immunosuppressive treatments were reserved for patients not responsive to splenectomy. These advancements have been incorporated in two international current guidelines: the first, produced by an international group of expert clinicians (International Consensus Report, ICR); the second, by a selected group of hematologists and methodologists with expertise in systematic reviews and guideline development, mainly from United States, without direct connection with pharmaceutical companies. This latter guideline was endorsed by the American Society of Hematology (ASH). A new standardized terminology has also been adopted, with a more clear definition of primary vs secondary ITP and a clear distinction between the different phases of the disease: newly diagnosed, persistent, chronic (after 12 months from diagnosis). Both guidelines structure their suggestions on first, second and third-line treatments, with less attention to the different phases of the disease and its severity. There is a substantial agreement in proposing the initial treatment with oral corticosteroids and TPO-ra as third-line approach in patients unsuccessfully splenectomized in whom these agents appear to have the more favorable therapeutic profile. As to the second-line approach in patients failing corticosteroids, rituximab and TPO-ra could be valid alternatives to splenectomy but, unfortunately, the international guidelines fail to offer a consistent approach. Whereas ICR considers splenectomy at the same level of many other second-line treatments including rituximab and TPO-ra, ASH guideline definitely recommends reserving TPO-ra and rituximab to patients failing or with a contra-indication to splenectomy. As new data are being accumulated on long-term outcomes and toxicity of TPO-ra and the role of rituximab is being better defined for particular patients as second-line therapy, it will be possible to revisit the pros and cons of these options vs each other and splenectomy which, although less and less popular, maintains the highest curative potential, with an acceptable toxicity. The thrombotic risk in ITP should also be better defined and taken into account in guiding the treatment in the individual patients. Hopefully, new studies will be based more on clinical outcomes than on platelet count increase. The ultimate lesson of the insufficient evidence and disagreement among experts is that management of ITP should be tailored to the individual patients.
Up to 1996, when George et al., on behalf of the American Society of Hematology published a practice guideline (GL) (in short, ASH-1996 GL) [1] for diagnosis and treatment of Immune Thrombocytopenia (ITP), at that time called idiopathic thrombocytopenic purpura, no international guidelines were available for this disorder. ASH-1996 GL gained worldwide reputation and wide application. Splenectomy emerged as the most effective treatment with an acceptable safety profile, as further confirmed by a systematic review by Kojouri et al., restricted to adults [2]. Subsequently, Vesely et al. (again from George’s group) in their detailed review showed that none of the many treatments available for patients refractory to surgery had sufficient evidence to support their effectiveness and safety [3]. A consensus-based guideline produced and published under the umbrella of the British Society of Haematology in 2003 (in short, BCSH-GL) [4] also deserves consideration for its diffuse appreciation and updated review of literature. Two new major treatment options became available and gained diffuse use in more recent time: anti-CD20 chimeric human antibody (rituximab), primarily registered for the treatment of CD20 positive large cell lymphomas by Food and Drug Administration (FDA) in 1997 and subsequently proposed also for autoimmune disorders like ITP (reviewed in Arnold et al.) [5] and, in the last decade, a novel class of agents that increase platelet production by stimulating the thrombopoietin (TPO) receptor, currently known as TPO-receptor agonists (TPO-ra) [6]. These new treatments were considered in the international consensus report guidelines (ICR GL in short) [7] and in an update of previous ASH guidelines (in short, ASH-2011 GL) [8]. These more recent GL, particularly ASH-2011 GL, substantially adopted the standardized terminology, definition and outcome criteria proposed by an International Working Group (IWG) on ITP [9]. To facilitate the reader, a summary of this new terminology and related definitions is reported in box 1.

The discussion will be limited to diagnosis and management of ITP in adults focusing on those aspects with insufficient evidence and that remain unsettled or controversial. Table I summarizes the main characteristics of current GL.

A striking difference between ICR and ASH-GL is that in the ICR GL the different therapeutic options are strictly listed in alphabetical order so as to show no preference for a particular treatment. ASH document is more similar to traditional GL in that it offers a more detailed level of evidence and the strength of evidence is extensively used to recommend or suggest management options. Both documents emphasize the limited number of randomized clinical trials comparing the outcome of different treatments in terms of response rate and duration upon which to base clinical recommendations. Moreover, the treatment should be tailored to the individual patient taking into account the presence and severity of bleeding, the rapidity of response and the expected side effects and costs. A more in-depth and critical comparison of ICR and ASH 2011 GL has been recently published [10].

**Diagnosis**

Primary immune thrombocytopenia identifies an autoimmune disorder characterized by an isolated platelet count < 100 x 10^9/L with or without bleeding manifestations, in absence of other causes or disorders that may be associated with thrombocytopenia. Recommendations for the diagnosis of ITP do not present major differences between the different GL. The recommendations of the ICR, in which children and adults are considered together, may represent a good synthesis of the current accepted practice for diagnosis of ITP and the reader is referred to this report. Some points deserve further attention.

At variance with previous GL, which suggested bone marrow examination in selected patients, that is older than 60, before splenectomy in adults, before corticosteroid administration in children, in unresponsive to intravenous immunoglobulins (IVlg) [1,4], a different position is taken in the more recent ASH-2011 GL. It recommends that for children and adolescents bone marrow examination “is not necessary” in cases with the typical features of ITP, even in those not responding to IVlg (grade 1B) and suggests that bone marrow is not necessary also before starting treatment with corticosteroids or before splenectomy (grade 2 C). For adults, it suggests that bone marrow examination is not necessary in cases with typical ITP irrespective of age (grade 2 C). In our policy, a bone marrow aspiration is usually carried out under local anesthesia to immediately exclude blood malignancies for patient or patient’s family reassurance. The investigation of platelet survival and site of platelet sequestration using indium-labeled autologous platelet scanning is currently considered of uncertain benefit. This view has been supported by a recent literature review [11]. Search for antiplatelet antibodies remains controversial and
Box 1

Immune Thrombocytopenia (ITP): definitions and terminology.

**Primary ITP**
- Autoimmune disorder characterized by isolated thrombocytopenia (platelet count in peripheral blood < 100 x 10^9/L) with no other causes or disorders that can be associated with thrombocytopenia
- Primary ITP is a diagnosis of exclusion; at present there are no reliable clinical or laboratory parameters that allow accurate diagnosis
- The main clinical problem of primary ITP lies in the increased risk of bleeding, although bleeding symptoms may not always be present

**Secondary ITP**
- All forms of immune thrombocytopenia, except for primary ITP*

**Stages of the disease**
- Newly diagnosed ITP: within the first three months following diagnosis
- Persistent ITP: between 3 and 12 months following diagnosis. This includes patients who have spontaneous remissions or whose complete response at the end of the first therapy is not maintained over time.
- Chronic ITP: lasting more than 12 months

**Severe ITP**
- This term indicates cases with bleeding symptoms at onset which require therapeutic intervention, or with development of new bleeding symptoms that require additional therapy with different treatment or a higher dose

**Refractory ITP**
- Two criteria have to be fulfilled at the same time: the lack of response or relapse after splenectomy with severe ITP or a bleeding risk that needs treatment according to the GP
- Temporary response to corticosteroids or to intravenous immunoglobulins does not exclude a refractory form
*The acronym ITP is followed by the name of the associated disease in brackets, for example: secondary ITP (associated to Lupus); secondary ITP (associated to HIV); secondary ITP (drug-induced). In titles of manuscripts, abstract, shortened forms can be used such as lupus-associated ITP or HIV-associated ITP, etc.

Testing is not suggested by the ASH-2011 GL, while the BCSH-GL admits its utility in some refractory cases. *H. Pylori* testing is considered worthwhile in refractory patients by the BCSH-GL, whereas in ICR GL the detection of *H. Pylori* infection, preferably by urea breath test or stool antigen test, should be considered at baseline. ASH-2011 GL only states that this test is not necessary in children. The presence of antinuclear antibodies (ANA) may indicate a propensity to develop autoimmune disorders. The occurrence at diagnosis of antiphospholipid antibodies (APA) or lupus anticoagulant (LA) in patients without a history of thrombosis in the last months and with no evidence of additional autoimmune manifestations may be evident in up to 30% of cases. It remains to be investigated by prospective studies if these patients, still to be considered having primary ITP [9], will deserve a different prognosis and/or treatment.

**Management**

We shall mainly consider the most recent international guidelines (ASH-2011 and ICR) since they are updated to consider the newest treatment approaches and to adhere as much as possible to the accepted international nomenclature of this disease, making narrative reference to particular relevant publications for specific issues. Inferences regarding the efficacy of treatment will continue to be based mainly on platelet count as the more reliable surrogate outcome measure.

**Who should be treated?**

There is substantial agreement, despite different formulations, that treatment, at least in newly diagnosed patients, is indicated in presence of bleeding manifestations or anyway if platelet count is below 30 x 10^9/L. In absence of bleeding, a platelet count of 20 x 10^9/L is a compelling case for treatment [12]. Standardized description of bleeding symptoms and gradation of their severity, as proposed by the IWG on ITP [13], could facilitate a more consistent approach in deciding which patients need treatment and better dictate the type of treatment. A symptom-based approach has already proved useful in deciding the most appropriate management in critical situations that could demand immediate treatment with high-dose IVIg, platelet transfusion or hospital admission [14]. Better predictors of bleeding risk and individualization of indications according to age, gender, concomitant medications, life-style and patient’s expectations should be addressed by future studies. An emerging issue is represented by patients presenting with ITP while taking or requiring some form of antithrombotic medication, a situation increasingly encountered in clinical practice.

**Newly diagnosed ITP**

Treatment is aimed at rapidly obtaining a safe platelet count to prevent or stop hemorrhages and to ensure an acceptable quality of life, avoiding as much as possible treatment-related adverse effects. Corticosteroids, IVIg or anti-D Ig are considered first-line treatments by ICR [7] and ASH-2011 [8]. Corticosteroids remain the mainstay of treatment and prednisone 1 mg/day for 3–4 weeks followed by tapering in another 2–3 weeks is a general standard approach. Some treatments have been proposed with the aim of increasing the response rate and duration of response. A definite advantage of high-dose
Dexamethasone is not demonstrated in terms of response duration over 6–12 months [15–17] and should be prospectively further investigated. Rituximab, with or without steroids, has failed to demonstrate a significant improvement over conventional treatments in newly diagnosed patients or any way a clear net benefit overcoming its adverse events [18].

**Persistent ITP: a neglected area in current GL**

Patients still remaining thrombocytopenic after 3 months from diagnosis or initial treatment are classified in two distinct phases: persistent (between 3 to 12 months) or chronic after at least 12 months since they may still obtain a long-term remission or be apparently cured mainly during the first 12 months or even later [19]. Thus splenectomy, once more liberally proposed [1] is currently reserved for patients still requiring treatment after one year or more from initial treatment. Unfortunately, none of the available GL specifically addresses patients with persistent ITP (as no data are available in literature apart from anecdotal evidence in sparse cases). In both ICR and ASH-2011 GL, patients not responding to first-line treatments (corticosteroids, IVIg, anti-D) are lumped together in a single heterogeneous category irrespective of the different phases of disease (newly diagnosed, persistent or chronic ITP).

This precludes separate considerations for patients failing initial corticosteroids but still with a short disorder duration – and thus at a more favorable prognosis – from those with a more advanced disease and thus probably already exposed to more lines of medical treatments. Both GL just suggest that, if splenectomy is deemed necessary, surgery should be deferred for at least 6 months (ICR) or 12 months (ASH-2011) from diagnosis.

Considering that 50 to 80% of initially treated patients will relapse and require further treatment after failing initial corticosteroids, the most appropriate treatment of patients with persistent ITP represents an area of major clinical interest burdened by unacceptable uncertainty. A general rule is to spare these patients treatments with long-term adverse effects such as prolonged use of corticosteroids, immunosuppressive drugs or chemotherapy. Sometimes, on demand therapy is the only treatment used at the time of or in anticipation of high risk bleeding situations. In other cases, the lowest effective dose of corticosteroids is maintained for weeks or months [12]. Dapsone, an inexpensive drug with a well-established safety profile, could also prove useful in this setting [20]. Danazol administration could also be a useful alternative [21] to spare corticosteroids until a decision on splenectomy has, eventually, been taken.

### Table 1

<table>
<thead>
<tr>
<th>GL (year)</th>
<th>Panel</th>
<th>Method for analysis consensus</th>
<th>Pros</th>
<th>Cons</th>
<th>Utility in difficult cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASH-GL (1996)</td>
<td>15 professional members from USA and Canada only COI not disclosed</td>
<td>Explicit, by voting Rank of agreement provided</td>
<td>Detailed and complete. Endorsed by ASH</td>
<td>Not of immediate readability. Offers clear directions to clinicians National GL</td>
<td>Major in most circumstances</td>
</tr>
<tr>
<td>BCSH-GL (2003)</td>
<td>9 professionals from UK only COI not disclosed</td>
<td>Not explicit</td>
<td>Detailed and complete Updating from ASH-GL Endorsed by BCSH</td>
<td>Not of immediate readability National GL</td>
<td>Major in most circumstances</td>
</tr>
<tr>
<td>ICR (2010)</td>
<td>20 professionals International representation. COI disclosed</td>
<td>Not explicit</td>
<td>Detailed and complete if appendix considered. Offers the most updated summary of available evidence</td>
<td>Not of immediate readability Less directive in providing advice International GL</td>
<td>Major in most circumstances Requires consideration of the electronic appendix</td>
</tr>
<tr>
<td>ASH-GL (2011)</td>
<td>7 professionals (3 experts in ITP management) without COI 12 professionals with COI as reviewers only</td>
<td>Not explicit</td>
<td>New terminology adopted Recommendations only if evidence-based Endorsed by ASH Impartiality</td>
<td>Gray areas not addressed Most emphasis on evidence less on clinical expertise International GL, mainly US</td>
<td>Minor utility in complex cases</td>
</tr>
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</table>

However, with the advent of TPO-ra which have a response rate in 60–70% of cases and are apparently devoid of major short- or medium-term toxicity [22–24], one could consider to treat with these agents patients at risk of bleeding while in persistent phase as a bridge to splenectomy, thus sparing them more toxic agents or more demanding treatments like in-hospital administration of IVIg. This approach will allow to safely manage patients while waiting for a possible remission, either spontaneous or facilitated by these agents as recently suggested [25,26], or to take a definite orientation towards a treatment with curative potential like splenectomy or rituximab. This is clearly an area that deserves further studies.

Patients not responding or relapsing after corticosteroids or other first-line therapies

A striking difference between ICR and ASH-2011 GL consists in the different position assigned to splenectomy in the treatment strategy. ICR GL reports in alpha order a list of several second-line treatments which includes splenectomy together with many medical therapies such as azathioprine, cyclosporine A, dapsone, mycophenolate mofetil, rituximab and TPO-ra, vinca alkaloid. All these options, including TPO-ra, are purposely listed in alphabetical order so as to show no preference for a particular therapy. Noteworthy, the ICR experts did not find consensus (or evidence) for preferring splenectomy over any of the considered second-line medical treatments despite acknowledging that surgery could produce up to 66% of sustained responses after 5 years. Consequently, TPO-ra, a treatment that requires continuous, possibly lifelong administration and is currently approved only for chronic ITP, and whose long-term effects are not yet fully evaluated [22–24] is placed in ICR proposal at the same level of evidence as splenectomy. However, when it comes to patients failing first and second-line therapies, without any mention if they were splenectomized or not, ICR GL makes a recommendation of category A in favor of TPO-ra. This position has been overtly criticized [27]. A further element of perplexity consists in failing to consider the different aims of “single-shot” treatments aimed at obtaining long-term or indefinite remission, like splenectomy and rituximab, with the “maintenance” approach of TPO-ra.

At variance with ICR GL, ASH-2011 GL, acknowledging that splenectomy remains the only treatment that provides sustained remission without a concomitant therapy in a high proportion of patients, places splenectomy as a turning point in deciding further treatments in patients with chronic ITP. ASH-2011 GL recommends splenectomy for patients who have failed corticosteroid therapy and TPO-ra only if they are at risk of bleeding and relapsed after splenectomy (thus following the definition of refractory ITP by the international working group for ITP) [9] or have a contra-indication to splenectomy and have failed at least one other therapy. Both recommendations receive grade 1B. Noteworthy, these recommendations are in keeping with the European Medicine Agency (EMA) approved indication for TPO-ra but not with the FDA, which is in agreement with the recommendations of the ICR GL. In ASH-2011 GL, rituximab and TPO-ra are suggested for consideration with grade 2 C in patients at risk of bleeding who have either failed one line of therapy such as corticosteroids, IVIg, splenectomy or rituximab or did not undergo splenectomy (TPO-ra).

In general, the published guidelines do not provide a practical algorithm of preferred treatment sequence in chronic ITP. To address this limitation, Ghanima et al. [28] recently presented an instructive clinical case-study followed by an in-depth discussion of the pros and cons of the three major treatment modalities in chronic ITP including splenectomy, TPO-ra and rituximab. The authors’ main conclusion is that treatment should be individualized, with an active participation of the patients to the decision-making process, considering several individual factors like bleeding history, comorbidities, concomitant therapies, life-style, expectations and compliance.

Refractory

Refractory patients are defined on the basis of two criteria [9]. First, they should have failed splenectomy or have relapsed thereafter. Second, they should either exhibit severe ITP (clinically relevant bleeding) or have a risk of bleeding that in the opinion of the attending physician requires therapy. The aim of treatment in these patients should be to maintain a platelet count sufficient to prevent clinically significant bleeding. Both recent GL agree to recommend TPO-ra acknowledging the efficacy of these agents, in term of platelet increase and reduction of bleeding symptoms, also in patients who have failed splenectomy and second-line medical treatments. It can be estimated that a few percentage of patients (around 3–5%) of those initially responding to same first or second-line treatments including splenectomy, TPO-ra and rituximab ultimately fail to respond to almost all available therapies and remain with a platelet count below 10–20 × 10⁹/L. These patients are at very high risk of severe or even fatal bleeding [29,30], current GL do not provide any indication and ICR GL just mentions some treatments (campath-1H, combination chemotherapy and hematopoietic stem cell transplantation) emphasizing their associated considerable toxicity and the very limited evidence supporting their use. Novel agents are eagerly awaited [15].

Special considerations and conclusions

Primary ITP still remains a diagnosis of exclusion and no clinical or laboratory marker is able to predict the future natural history in the individual patients. In particular, the clinical relevance of testing for H. Pylori, APA/LA or ANA remains unsettled. It is
apparent from our discussion that current GL fail to provide an unanimous consensus on the best management approach, particularly in patients failing first-line treatments, and that several issues demand further investigation. Moreover, an open criticism has been expressed on the methodological issues that should inform the production of GL, with a specific reference to ITP [10]. The place of splenectomy remains disputed, despite it is the only “curative” approach with two thirds of patients remaining in remission for more than 10 years from surgery [31], with minimal/moderate toxicity [24]. The possible increased risk of thrombosis in ITP is currently debated. In a retrospective evaluation of one thousand patients with ITP requiring at least one line of treatment in 7 referral centers in Italy [32] the arterial and thrombotic risk was only slightly increased, while it was higher in splenectomized patients with an hazard ratio of 3.5, in keeping with a large retrospective study conducted in USA on the basis of administrative data [33]. The risk of thrombosis in ITP, particularly in splenectomized patients, should thus be considered before undertaking other treatments associated with increased thrombotic risk. It is still not fully clarified if this is the case with TPO-ra. In fact, a surprisingly higher annualized risk of thrombosis was apparently reported in patients treated with TPO-ra [22–24]. Of course, the finding that some patients treated with TPO-ra may achieve a response or complete response of variable duration after their suspension, although still limited to a thin percentage of patients, is encouraging and may favor their use before splenectomy. However, “spontaneous” improvements of ITP are described even after 2 or 3 years from diagnosis in non splenectomized patients as shown by a large retrospective observational study, aimed at calculating the incidence of complete or partial remissions in a cohort of 114 adult patients with severe ITP during a long follow-up [19]. In this study, a response rate higher than 80% was reported in non splenectomized patients, so that the authors suggest that splenectomy may be delayed for up to 3 years, when the chances of remission become very low.

Future trials on ITP treatment should possibly focus more on bleeding manifestations and related morbidity than on just correcting platelet count. We should be aware that platelet count is a surrogate endpoint with several limitations that does not immediately translate into a substantial clinical benefit, particularly if the treatment-related toxicity is relevant. A Cochrane review criticized the results of clinical trials with TPO-ra due to the lack of clear evidence of their ability to reduce major bleeding and to improve survival. While this criticism should not be over emphasized, [34] a better balance could be achieved among the various stakeholders involved in the process of approval and assessment of new treatments for ITP [35–38]. In this regard, EMA is preparing new guidelines for future trials.

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