Immune thrombocytopenia (ITP) includes different entities characterized by increased destruction or diminished production of platelets mediated by antibodies against platelet or megakaryocyte membrane antigens. According to the current nomenclature, ITP is defined as secondary (secondary ITP) when there is evidence of an underlying disease as opposed to primary (primary ITP) when no associated disorder can be demonstrated at the time of diagnosis.1

Lymphoproliferative disorders (LPDs) are recognized as a common cause of secondary ITP. Approximately 30% of secondary ITP cases are present on diagnosis of lymphoid tumors or develop during the course of the disease.2,3 Among the different LPDs, ITP has the highest prevalence in chronic lymphocytic leukemia (CLL),4 ranging between 2% and 5%.5–8 It is far less frequent in non-Hodgkin lymphoma and Hodgkin lymphoma (HL), where its prevalence is invariably reported to be below 2%.4,9–14

Because of its rarity, the clinical behavior and response to treatment of secondary ITP in LPDs has been poorly investigated. A correlation between the survival of patients with LPDs and the occurrence of autoimmune phenomena directed against hematopoietic cells has been observed4 but not confirmed.12 Diagnosis of ITP associated with LPDs may be difficult at times, given that many confounding events are known to variably reduce the platelet count in addition to diffuse bone marrow infiltration by malignant lymphocytes. Moreover, reversible thrombocytopenia may be induced by the toxic effects of chemotherapy. The lack of sufficient sensitivity and specificity of platelet autoantibody tests (which parallel the direct Coomb test for
red blood cells in hemolytic anemias\textsuperscript{15,16} certainly hampers the interpretation of some acute thrombocytopenias. Reliable and standardized clinical criteria are needed to distinguish ITP from other immune and nonimmune causes of thrombocytopenia. In contrast to primary ITP, patients with secondary ITP and LPDs are usually older and have lower initial platelet levels because of concomitant cytotoxic treatments. The specific therapy for ITP may negatively interfere with the chemotherapy program or aggravate the already present immunosuppression. A correct diagnosis and an adequate therapeutic approach may prevent life-threatening bleeding, avoid undue toxicity, and be life-saving.

The pathogenesis of secondary ITP is usually mediated by IgG autoantibodies that coat platelets, inducing their accelerated clearance by the spleen and the liver, or impair megakaryocyte platelet production, as in primary ITP. Although platelet-reactive antibodies may be responsible for platelet destruction in the course of LPDs, several other mechanisms have been described that may interfere with platelet production. Direct inhibition of megakaryocyteopoiesis by cytotoxic T cells or by inhibitory cytokines and complement-mediated platelet destruction by IgM may explain the platelet decrease seen in different T- and B-cell neoplastic diseases. Dysregulation of the microenvironment induced by soluble factors secreted by malignant cells and the consequent T-cell dysfunction have been shown to be crucial for the emergence of autoreactive clones.\textsuperscript{7,17} Furthermore, drugs commonly used in the treatment of LPDs (eg, fludarabine) have also been associated with an increased risk of developing ITP because of their different cytotoxic effects on T- and B-cell differentiation and survival.

ITP ASSOCIATED WITH CLL

\textit{Epidemiology and Diagnostic Criteria}

Approximately one fourth of patients with CLL experience an autoimmune complication,\textsuperscript{17} primarily autoimmune hemolytic anemia (AHA) or ITP. By pooling heterogeneous data from different series, it has been estimated that ITP complicates the course of CLL in about 2\% of patients.\textsuperscript{7,17} Recently, a higher prevalence of ITP (5\%) was reported in a series of 1278 patients newly diagnosed with CLL consecutively referred to three major hematology institutions in Italy.\textsuperscript{8} This estimate was based on standardized clinical criteria to exclude other causes of thrombocytopenia. Briefly, the diagnosis of ITP required all of the following criteria: rapid (<2 weeks) and severe fall (at least half of the initial level and below $100 \times 10^9$/L) of the platelet count; a normal or augmented number of megakaryocytes in the bone marrow; an absence of splenomegaly on physical examination; and no cytotoxic treatments in the last month. A lack of response to platelet transfusion (in patients without known refractoriness to platelet concentrates) or a rapid response (<1 week) to high-dose intravenous Ig (IVIg) were considered essential requirements for the diagnosis of ITP in patients with advanced Rai or Binet stage (3–4 or C) and extensive bone marrow involvement.

\textit{Biology}

CLL is a mature B-cell neoplasm coexpressing the T-cell antigen CD5 and B-cell surface antigens CD19, CD20, and CD23. The biology of the disease is complex, and the cell from which CLL is derived has not been determined. The leukemia cells express immunoglobulins that may or may not have incurred somatic mutations in the immunoglobulin heavy chain variable region genes (IgVh), suggesting that CLL is more heterogeneous than previously suspected.\textsuperscript{18}
CLL is typically characterized by profound immunosuppression, with T-cell function impairment and insufficient antibody production already manifest in the early phases of the disease. As a consequence, patients experience frequent infections, autoimmune cytopenias, and a relatively high rate of second tumors. T-cell functional defects may be caused by pathologic inhibitory cytokines (interleukin-10 and transforming growth factor-β) or by inappropriate interactions of normal T and B lymphocytes with CLL B cells. The altered function of the immune surveillance system and of regulatory T cells (T-reg) facilitates the emergence of B-cell clones producing autoantibodies. The inhibitory signals that the CLL B cells deliver to T-reg cells seem to prevent the elimination of nonneoplastic autoreactive T and B cells. Hence, the autoreactive antibodies are polyclonal and not secreted by the malignant clone.

Cytotoxic treatment may further complicate the homeostasis of the immune system. Fludarabine has been associated with the occurrence of ITP in the course of CLL and other chronic diseases, but cladribine and pentostatin have also been described to be associated with autoimmunity, possibly caused by the profound T-cell suppression, toxic effects on T-reg cells, and altered CD4/CD8 ratio induced by these drugs. The same mechanism has been implicated in Campath-related ITP.

IgVh DNA sequence analysis of CLL B cells has revealed a significantly higher risk for patients with unmutated cells to develop ITP. Unlike their mutated counterparts, whose B-cell receptor is quiescent and unable to transmit external signals to the cell nucleus, unmutated CLL B cells usually remain responsive to external stimuli and are capable of binding multiple antigens, including autoantigens, which promote their survival and proliferation. Unmutated CLL B cells have an increased ability to phosphorylate p72 (Syk) and Zap-70 molecules in response to sIgM ligation by an antigen, providing evidence for an intact downstream signaling pathway of their B-cell receptor. The more aggressive clinical behavior of unmutated CLL B cells might be related to frequent (auto) antigenic interactions with their B-cell receptor. The preferential occurrence of ITP and AHA and isolated positive direct antiglobulin tests in unmutated patients suggests that unmutated cells also favor the emergence of autoimmune diseases.

A bias toward the Vh1 gene family has recently been observed in patients with ITP and CLL (43%) compared with patients without ITP (21%; \( P < .01 \)). More interestingly, the Vh4 family, usually found in approximately 20% of CLL cases irrespective of mutational state, was found in 22% of patients without ITP, as expected, but in only 4% of patients with ITP (\( P = .02 \)). The finding of a preferential Vh-gene distribution leads to the speculation of a possible antigen-driven process in ITP pathogenesis in these patients.

**Clinical Impact**

ITP seems to be equally distributed among the different CLL stages, with a median age of 68 years and a male predominance. Unlike AHA, the occurrence of ITP seems not to be temporally related to tumor progression or recurrence, with most patients developing ITP after a median time of less than 2 years from diagnosis, whereas CLL is stable and patients have not initiated therapy. Among patients with ITP associated with CLL, 8% have been reported to have experienced World Health Organization grade 4 bleeding episodes, and most of them died of this complication. Bleeding complications, however, have not been systematically assessed thus far.

Both Rai and Binet staging classifications recognize a platelet count less than 100 × 10^9/L at CLL diagnosis as a very unfavorable prognostic factor, regardless of the etiology of the thrombocytopenia. Based on survival results from a few small series, the impact of ITP on overall CLL prognosis has been questioned, supporting...
the idea that thrombocytopenia is an adverse prognostic marker only when reflecting extension of the disease.

In contrast, the occurrence of ITP itself was a strong negative prognostic factor for patients with CLL in a series of 1278 newly diagnosed patients with CLL. As shown in Fig. 1, patients with thrombocytopenia on CLL diagnosis did poorly regardless of the etiology of the low platelet count. Contrary to common belief, their prognosis was similar to patients with a low platelet count caused by tumor infiltration according to Rai and Binet classifications (Fig. 2). Multivariate analysis also indicated that the occurrence of ITP within 24 months of CLL diagnosis and its refractoriness to treatment had a further independent negative impact on overall survival.8

**Treatment**

Little is known about the treatment of ITP in the course of CLL. Some studies have reported that ITP of CLL can be successfully treated with steroids,30 cyclosporin A,31 or splenectomy,28 with a variable duration of response. Furthermore, long-term responses have been described after treatment with cytotoxic agents32,33 or anti-CD 20 monoclonal antibodies (rituximab).34–36 According to the authors’ experience, when these patients are treated with conventional therapies used for primary ITP, a far less favorable response rate is observed.8,37 In their patients a response to steroids occurred in 52% of patients, which is in the lower range of response rates to steroids reported for ITP (50%–75%). Furthermore, although approximately 80% of ITP patients usually respond to IVIg, only half of patients with ITP and CLL responded to IVIg alone. Splenectomy seemed effective, however, with 70% of patients experiencing a long-term response. A total of 14 (22%) patients were refractory to all administered treatments. This number is greater than what has been reported for adult ITP cohorts (9%).38 Most patients require treatments directly targeted to the tumor.

Rituximab, which is known to be active in both CLL and ITP, needs to be further investigated in ITP associated with CLL, particularly in light of some promising preliminary results.34,35 Rituximab therapy has also been reported to be effective in fludarabine-associated ITP, which is often refractory to conventional treatments and may be

![Fig. 1](image-url)  
**Fig. 1.** Overall survival (OS) according to the development of ITP at any time. Survival curve of 64 patients with ITP and CLL compared with 1214 patients with CLL who did not develop ITP. (From Visco C, Ruggeri M, Evangelista ML, et al. Impact of immune thrombocytopenia on the clinical course of chronic lymphocytic leukemia. Blood 2008;111:1110–6; The American Society of Hematology; with permission.) Copyright © 2008 the American Society of Hematology.
a life-threatening complication.\textsuperscript{34,39} The most effective schedule is not clearly defined, and a lower dosage of 100 mg weekly for 4 weeks (compared with 375 mg/m\textsuperscript{2} or higher), which has shown promising results in primary ITP,\textsuperscript{40} deserves testing in patients with CLL and ITP. Rituximab may further deepen the immunosuppressed state, however, and favor potentially life-threatening infections.\textsuperscript{41}

\section*{ITP Associated with Non-Hodgkin's Lymphomas}

\textbf{Waldenström Macroglobulinemia}

Some monoclonal proteins from patients with Waldenström macroglobulinemia (WM) possess antigen-binding activity for autologous or foreign antigens. Autoimmune phenomena, such as cold agglutinin hemolytic anemia, mixed cryoglobulinemia, and peripheral neuropathy, are well-recognized complications of WM. In a prospective cohort of patients with WM who were extensively investigated for the presence of autoimmune phenomena, about half of the serologic and clinical manifestations of autoimmunity were present at diagnosis, whereas others appeared during the course of the disease.\textsuperscript{42} The prevalence of ITP in WM ranges between 3\% and 9\%.\textsuperscript{42,43} and a platelet-associated monoclonal IgM has been shown to be related to the occurrence of ITP.\textsuperscript{43–45} The size of the M-component was not correlated with ITP prevalence.\textsuperscript{42}

Complement-mediated thrombocytopenia may appear in association with monoclonal IgM antiplatelet antibodies.\textsuperscript{46} Together with antineoplastic drugs, plasmapheresis can be of value for temporarily treating selected patients with ITP and monoclonal gammopathy,\textsuperscript{47} whereas splenectomy does not seem to be a good option.\textsuperscript{46} Conventional treatments used for primary ITP do not seem to induce lasting remission of ITP secondary to WM.

\textbf{Monoclonal Gammopathy of Undetermined Significance and Multiple Myeloma}

Immune thrombocytopenia has only rarely been documented in patients with multiple myeloma.\textsuperscript{48–50} A recent series reported a prevalence of 2.6\% for secondary ITP in 228 patients with monoclonal gammopathy of undetermined significance. The monoclonal component was mostly of the IgG (71\%) or IgM type (18\%).\textsuperscript{51} Patients with monoclonal gammopathy of undetermined significance–associated ITP were older than
those with monoclonal gammopathy of undetermined significance without ITP, and no correlation was found between platelet response and variations in the M-component after B-cell clone directed therapies. Rituximab was tried in a single patient and was ineffective,\textsuperscript{52} whereas others reported short-lived responses to IVIg or steroids.\textsuperscript{49}

A shortened platelet half-life has been shown in patients with multiple myeloma,\textsuperscript{53} although no correlation has been found between platelet survival and paraprotein concentration. An intravascular process of platelet activation and consumption has been postulated, either as a result of platelet defects related to the presence of the paraproteinemia or as a consequence of the high platelet autoantibody levels that increase the susceptibility of platelets to degradation. Elevated platelet-associated immunoglobulin has been reported in patients with myeloma and is believed to be secondary to nonspecific binding of serum IgG to platelets, usually not resulting in clinically significant thrombocytopenia.\textsuperscript{54}

**Marginal Zone Lymphoma**

Secondary ITP has been reported quite frequently (in up to 5% of cases) in patients with marginal zone lymphoma (MZL) of the mucosa-associated lymphoid tissue or of the splenic type. A higher prevalence than other LPDs has also been reported for AHA and acquired coagulation disorders. These immune complications are typically found in patients without leukemic spread of the tumor or even preceding the diagnosis of lymphoma and seem to be associated with a higher risk of disease progression.\textsuperscript{55–58} In most cases, the platelet count improved with antilymphoma therapy.\textsuperscript{59,60} Refractoriness to steroids has frequently been reported.\textsuperscript{57,58} Regression of ITP after mucosal resection of the lymphomatous lesion of the mucosa-associated lymphoid tissue type has been described.\textsuperscript{51,62} The presence of monoclonal gammopathy of the IgM type, which is often encountered in this lymphoma subtype, might explain the more frequent finding of ITP in these patients.\textsuperscript{63}

**Other B-cell Lymphomas**

Follicular lymphoma and diffuse large B-cell lymphoma, which represent the most frequent forms of non-Hodgkin lymphoma, have rarely been associated with secondary ITP.\textsuperscript{4} Of note, an association with ITP has been occasionally described in aggressive lymphomas involving atypical extranodal organs (eg, kidney, heart, bladder, and mesentery).\textsuperscript{64–66} Improvement of the platelet count was not always accomplished with chemotherapy. Most of the ITP cases occurring in patients with diffuse large B-cell lymphoma and follicular lymphoma have been described after patients received an autologous transplant. The prevalence of ITP in this setting seems to be lower than 2%.\textsuperscript{67} Delayed immune reconstitution of T-rays and clonal expansion of CD8\textsuperscript{+} T cells may contribute to the development of ITP in this setting, without an association with the underlying disease or the type of conditioning regimen.\textsuperscript{68} Resolution of ITP is usually obtained by typical treatment, such as steroids or splenectomy, but ITP sometimes progressively resolves without specific treatment, possibly following immune reconstitution. Few cases have been reported of ITP associated with hairy cell leukemia,\textsuperscript{69,70} sometimes triggered by treatment with purine analogs. The pathogenesis of thrombocytopenia in these patients is difficult to interpret because relevant splenomegaly is one of the presenting features. As already reported for other forms of low-grade lymphoma, refractoriness to steroids is frequent. In mantle cell lymphoma, the occurrence of ITP seems extremely rare.\textsuperscript{9,71} Curiously, hairy cell leukemia and mantle cell lymphoma are the lymphoma subtypes most frequently associated with the occurrence of rituximab-related ITP, particularly when there is coexisting extensive bone marrow involvement or splenomegaly.\textsuperscript{72–76}
The mechanisms responsible for this form of thrombocytopenia have not yet been defined. Opsonization of platelets by soluble CD20 and a cytokine release syndrome seem the most convincing pathogenic hypotheses, whereas autoimmunity can be ruled out by the timing of the phenomenon. The platelet decrease usually spontaneously recovers within a few days but may be accompanied by a significant hemorrhagic syndrome.75,77

**T-cell LPDs**

ITP is an extremely rare complication of peripheral T-cell lymphoma,12 although some T-cell lymphoma subtypes have been frequently associated with autoimmune phenomena directed against hematopoietic cells. Both angioimmunoblastic T-cell lymphoma and hepatosplenic T-cell lymphoma may present with ITP, often associated with AHA,78-82 and should be treated upfront with aggressive chemotherapy protocols because of their dismal prognosis. The underlying state of immunodeficiency that characterizes these aggressive diseases and predisposes these patients to severe infections may be relevant for the pathogenesis of autoimmune phenomena.

Autoimmune neutropenia and immune-mediated anemia are common findings in large granular T-lymphocyte leukemia (T-LGL), which is characterized by clonal expansion of mature CD8+ T lymphocytes. Although severe thrombocytopenia has rarely been described in this condition,83 mild thrombocytopenia is common.84 Unlike other LPDs, the formation of autoantibodies is not implicated in peripheral platelet destruction in T-LGL because thrombocytopenia in these patients seems to derive from the suppression of megakaryopoiesis by LGL-mediated cytotoxicity. A defective Fas (CD95) apoptotic pathway has been related to the occurrence of autoimmunity in T-LGL, similar to what has been described for the autoimmune lymphoproliferative syndrome, an inherited disorder manifesting in childhood with autoimmune cytopenia, lymphadenopathy, and splenomegaly and characterized by the accumulation of double-negative (CD3+, CD4-, CD8-) T cells. In both diseases leukemic lymphocytes constitutively express Fas and Fas-ligand but are resistant to Fas-induced apoptosis.85 In addition, the accumulation of defective T cells interferes with immune tolerance. Treatment directed against the T-cell clone has been shown to resolve most immune complications. Methotrexate, cyclophosphamide, and cyclosporin A are the drugs most frequently adopted in this setting.86

**ITP ASSOCIATED WITH HL**

The prevalence of ITP in HL is around 0.5%. Nevertheless, many case reports have been described in the literature. In most cases, ITP occurred while lymphoma was in remission, after induction therapy had been completed, independent of the lymphoma activity.11,13,87-91 The median time from the diagnosis of HL to the development of ITP is about 2 years,13,87,88 although in rare instances ITP has been described at lymphoma presentation.92-94 The response to specific conventional treatments for ITP is usually good, and the development of ITP does not seem to modify the prognosis of the underlying disease.13,14,88 Although HL could be a predisposing condition, the characteristics, timing, and response to therapy of ITP associated with HL suggest that the underlying disease may have a minor influence on the development and course of the thrombocytopenia.

**DISCUSSION**

In the absence of an underlying disorder, most cases of acute-onset thrombocytopenia are grouped under the definition of primary ITP.1 The wide variability in response
to specific therapies and in the natural history of this disease suggests that primary ITP may not be a single entity and that certain cases may be triggered by underlying conditions that are not apparent, restricting the field of the pure idiopathic forms. Among secondary forms, ITP associated with LPDs is of particular relevance for its clinical impact and less favorable response to conventional treatments.

The true prevalence of ITP in the course of LPDs is unknown because of the lack of standardized diagnostic criteria and the insufficient diagnostic power of platelet antibody testing. The increase in bone marrow megakaryocytes, rapidity of the platelet fall, and absence of a previous recent cytotoxic treatment remain the most reliable diagnostic criteria.\(^8,17\) The recent demonstration of clonal CD5\(^+\)/CD19\(^+\) B-cell populations in the bone marrow of 16% of patients with primary ITP by flow cytometry\(^96\) is consistent with the hypothesis that some idiopathic cases might indeed be secondary to not yet clinically manifest LPDs. CLL is most frequently associated with ITP (2%–5% of cases). Unlike AHA, which has a very close relationship with CLL activity, ITP has a weak correlation with tumor activity.\(^5,8,11,27\) Although some small series did not describe an adverse effect of ITP on the survival of patients with CLL,\(^5,28,29\) a recent survey found ITP to be a strong adverse prognostic factor.\(^8\) Patients with ITP at CLL diagnosis did poorly, and their prognosis was similar to patients with a low platelet count because of tumor infiltration (Rai 4, Binet C; see Fig. 2). The impaired survival of CLL patients with ITP might be caused by the strong association between ITP development and unmutated IgVh status (81% in the authors’ series),\(^8\) which is widely known to discriminate tumors with aggressive behavior. Furthermore, immunosuppressive treatments purposely administered to treat ITP may increase morbidity and mortality because of infection.\(^97\)

The fact that ITP in the course of LPDs has different clinical characteristics and behavior than primary ITP is not surprising because it probably reflects the presence of different pathogenic mechanisms. Altered function of T-regs seems relevant in most of the cases of ITP arising in CLL, allowing the emergence of normal B-cell clones producing autoreactive antibodies against platelet antigens. Increasing evidence suggests that T-reg compartmentalization and trafficking may be modulated by chemokines and integrins secreted by the tumor.\(^98\) In WM and at least some MZL, the tumor produces monoclonal IgM with antiplatelet activity, which induces complement-mediated platelet destruction, an exceptional occurrence in primary ITP. T-LGL instead represents a paradigm for T-cell–mediated direct toxicity to platelets and megakaryocytes in the bone marrow.

Conventional treatments for ITP, such as those based on steroids, IVIg, and in select cases splenectomy, should be attempted first to rapidly control the thrombocytopenia. To produce lasting results or in case of failure of conventional treatments, however, which occurs in around 50% of cases, treatment directed against the malignant clone may be ultimately required. Table 1 summarizes the different therapeutic approaches and their correlation with the pathogenic background when ITP is associated with different LPDs.

Whatever the precise pathogenic mechanism causing ITP, whether mediated by autoreactive macroglobulins (WM, MZL) or by the cytotoxic effect of T cells (T-LGL) or when the malignant clone itself actively participates in the emergence of ITP (CLL), the most effective chemotherapy or immunotherapy against the tumor should be chosen. The second-generation thrombopoietin receptor agonist romiplostim (romiplostim and eltrombopag) recently introduced for treatment of primary ITP, however, yield very good results in increasing platelet count in over 80% of patients, and despite failure of several previous treatments, including splenectomy, raise new hopes. Indeed, irrespective of the precise pathogenesis, autoimmune antibodies negatively interfering...
with megakaryocyte platelet production are expected in most cases of ITP secondary to LPDs, not unlike what occurs in primary ITP. Ad hoc–designed prospective investigations are required to show the effectiveness of the agents for treatment of ITP associated with LPDs.

A more detailed understanding of the pathogenic mechanisms underlying the occurrence of ITP in different LPDs will drive targeted treatment decisions, avoiding unwarranted immunosuppression and bleeding complications.

**REFERENCES**


