Therapeutics, Pharmacology and Clinical Toxicology
Vol XIX, Number 1, March 2015
Pages: 25 - 28

THE MANAGEMENT OF THE AUTOIMMUNE THROMBOCYTOPENIA ASSOCIATED WITH CHRONIC MALIGNANT LYMPHOPROLIFERATIVE DISEASES

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Abstract. Autoimmune thrombocytopenia is a common immune hematologic complication associated with lymphoproliferative diseases, most frequent with chronic lymphocytic leukemia and non-Hodgkin's Lymphomas . The relation between autoimmune cytopenias and lymphoproliferative malignancies is well known and the mechanisms are complex. Regarding the ethiology, one or more simultaneously occurring causes could leed to thrombocytopenia. We should make a very riguros clinical and paraclinical judgement in diagnosis of autoimmune thrombocytopenia and then, treat not only the number of platelets but also manage the risk of significant bleeding. Supportive care , corticosteroids and chemo-imunotherapy are the currently used treatment , individualized for each pacient. The response to the lymphoma treatment is very good, and significant bleeding is rare.
Keywords: imune thrombocytopenia, lymphoproliferative diseases, antiplatelets antibodies

Introduction

Chronic malignant lymphoproliferation are associated with autoimmune thrombocytopenia (ITP) 1-5% in chronic lymphocytic leukemia (CLL) [1, 2], 0,76% in Non-Hodgkin Lymphoma (NHL) [3], 0,29% in Hodgkin Lymphoma (HL) [4].

CLL is the most often lymphoproliferative disease associated with autoimmune disorders . ITP complicate the course of limphoproliferative diseases, but also may precede the diagnosis (in CLL flow citometry of older pacients with ITP releved CD19/C5+ lymphocytes)[1,2].

Heterogenous histopatologycal forms of NHL are more frequent associated with ITP like: diffuse large B-cell lymphoma (DCLL) , small lymphocytic lymphoma, marginal zone lymphoma, waldenstrom disease/ myeloma, follicular lymphoma, mantle cell lymphoma; T cell lymphomas and lymphomas after autologous stem cell transplantation [3].

In Hodgkin's disease ITP take place most frequent in active phases or in periods of complete remission. The most important characteristics of the pacients are: old age , advance disease and non - nodular sclerosing histology[1, 4].

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Ethio - pathogenesis

Immune thrombocytopenia is a complex disorder of immune disregulation wich cause the autoantibody production[5, 6, 7]. The pacient underlying condition could perturbed the immune system before the onset of ITP , but also a pacient with one autoimmune disease is a high risk to develop a second [8] (was found CD 19/ CD 5 + clones in bone marrow from older CLL patients with ITP)[9].

Thrombocytopenia may reflect a part of immunological imbalance, closely related to the pathophysiological background of lymphoproliferative disease (HL, NHL)[4, 5]. In some cases the platelet antibody could be produced by lymphoma tissue itself (was demonstrated IgM platelet antibodies in lymphoplasmacytic lymphoma[3].

Beside the implication of B and T cells in auto-antibodies production (CD8+ cytotoxic T-cells from patients with active ITP antibodies bound and lysed platelets in vitro [10], another components of the immune system are disturbed : the reticuloendothelial system, receptors on monocytic phagocytic cells [3,5,7,8] (was found increased levels of BAFF = B cell activating factor, part of the tumor necrosis factor family [7,11]), and the complement (was observed complement-dependent lysis of platelets in vitro)[10].

It was observed that the autoantibody production in secondary ITP has the same mechanism of platelet destruction as in primary ITP [1] and include: production of antiplatelet antibodies by B lymphocytes against 2

groups of glycoproteins: GPIIbIIIa and / or the GPIbα, expressed on platelets and also on megakaryocytes,

- peripheral autoimmune destruction of platelets by increased platelets removal and phagocytosis by splenic macrophages,
- reduced bone marrow megakaryocyte production [6,8] by suppression of maturation , increased phagocytosis , alteration in megakaryocyte apoptosis , and
- disturbances in metabolism of trombopoietin (TPO) and its receptor, c-Mpl. These are the regulators of megakaryocytes and platelets production, with important roles in the differentiation of hematopoietic stem cells [12] (levels of TPO plasma are not elevated in patients with ITP) [10].

Diagnosis

It is considered that the diagnosis of autoimmune thrombocytopenia is more a diagnosis of exclusion[5,6]. If thrombocytopenia appear in the course of the lymphoproliferative disease it can have simultaneously multiple causes, like: chronic hypersplenism/splenomegaly, bone marrow infiltration or/and autoimmunity, but also recent treatment – chemotherapy (especially the use of purine analog - Fludara) or heparin treatment[2, 9].

The international working group recommend platelet value of < 100.000/mm^3 on peripheral blood count for the diagnosis of immune thrombocytopenia[2,3,5].

In CLL - thrombocytopenia is associated with IV stage (RAI classification) - secondary to bone marrow infiltration . It could be considered immune mediated when appear a rapid (< 2 weeks), important (half of initial number) and "unexplained" fall in platelet count [2,9], associated with the absence of splenomegaly on physical examination and no cytotoxic treatments in the last month[13].

There is no "gold standard" test that can reliably establish the diagnosis . [14] Platelet antibody detection test is not recommended at first intention because it shows an increased variability, and poor sensibility (platelets - associated IgG (PaIgG) are elevated in both immune and non-immune thrombocytopenia)[5,14]. Beside malignant lymphoproliferative disease the pacient coud have also immune conditions like chronic infections (HIV and hepatitis B, C) and autoimmune diseases (ex. systemic lupus erythematosus)[2,5]. In this regard it is necessary to thoroughly analyze the clinical and laboratory dates . Some tests have potential utility: glycoprotein specific antibody, antinuclear, antiphospholipid and antithyroid antibodies, a positive direct red-cell antiglobulin test [6,14]; another uncertain benefit: serum trombopoietina, PaIgG, bleeding time, platelet survival, serum complement[14].

Proper diagnosis and treatment of the underlying disorder play an important role in patient management.

The relation between ITP and common prognostic factors

The development of ITP in pacients with CLL was associated with a high white blood cell count (WBC), a positive DAT, unmutated genes of immunoglobulin heavy chain (IgVH) , ZAP70+ [2, 15, 16].

The occurrence of stereotyped configuration of B cell receptor (BCR) - HCDR3 (subsets 1 and 7) was associated with shorter time to ITP development compared to other patients[17]. Early appearance of ITP in the course of CLL and refractoriness to treatment were associated with the poorest outcomes[15]. The overall survival of patients with autoimmune cytopenia as a whole was not significantly different from the patients without this complication[18].

In CLL patients – in contradiction to autoimmune hemolytic anemia , ITP is not view like a complication of advanced disease[1,15]. Severe autoimmune thrombocytopenia is not correlate with active CLL disease[1]. ITP in CLL patients is associated with poor survival, but independent of the common clinical prognostic variables[16].

In Hodgkin lymphomas, pacients who presented with autoimmune cytopenias had a particular demographic and disease - related profile in contrast with the other, (not differ significantly from those who did not associated ITP)[4, 19].

ITP therapy

There is currently no consensus for a therapeutic approach to lymphoma - ITP[20]. The treatment in secondary ITP is often the same to the one used for primary ITP, but the management must be focused to obtaine a complet remission of the lymphoid malignancy and not to treat the decreased platelet number[1]. Indication for treatment: platelets <20/30.000/mm^3, active bleeding or high bleeding risk associated with platelets < 50.000/mm^3[5,6].

There are several parameters that must take into consideration (beside the platelet number): age, bleeding symptoms, health-related quality of life, side effects associated with therapy, the urgency of chirurgical procedures: simple or complex extraction (the platelet count recommended are > 30/50.000 /mm^3) , minor or major surgery (>50/ 80.000 / mm^3)[5, 6].

Traditional first-line therapy of ITP include corticosteroids, intravenous imunoglobuline (IVIG) and imunoglobuline antiRh (D) (the last two treatment are rare used in current practice - mainly due to high cost). Corticosteroids (Prednisone 1-2mg/ kg /day) for 4 weeks are the standard initial treatment in primary or secondary ITP[5, 14].

- In CLL response to first-line treatment, usually steroids or IVIg, is ~50 % to 60 %; about 20% are refractory [15]. The immunosupresion of this treatment could increased morbidity and mortality due to infections in CLL. Rituximab, monoclonal antiCD20antibody is known to be active in both CLL and ITP, needs to be further investigated in ITP associated with CLL[2,5].Vincristine is effective in some cases given at 1 mg weekly for 4 to 6 weeks[15].
- In Hodgkin lymphomas - ABVD combination chemotherapy (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine) provided effective control of HL and the autoimmune condition[3,4].
- In NHL patients, prednisolone alone is often inef-

fective, and chemotherapy for the lymphoma is recommended . The corticosteroids and Rituximab are included in most imunochemotherapy regimens used in NLH or in CLL: COP (Ciclofosfamida, Vincristin, Prednison)/ and /or Doxorubicina (CHOP) / Etoposide (COEP) and /or Rituximab (R) with good recovered of ITP after lymphoma treatment [3,5].

The second line therapy include splenectomy, rituximab-monoclonal antiCD20antibody and thrombopoietin - receptor agonists (TPO-R): Romiplostim and Eltrombopag[5].

In primary ITP splenectomy was considered the only "curative"therapy, but it side effects like sepsis, infections or possible vascular complications determine that pacients and doctors don't accept splenectomy as therapy for ITP[5]. In NHL - ITP was observed that splenectomy is effective in small lymphocytic and splenic marginal zone lymphomas, with a partial response in DLCL lymphoma[3].

The role of Rituximab (one dose/month or 4 doses/month) was studies in many randomized trials, recognized its application in many autoimmune conditions. In CLL has been used with good results [5,15]. Was reported high response rates using as initial therapy the combination of Rituximab with high-dose dexamethasone[14]. Is not clearly defined the most effective dose , a recent study in non - CLL - associated ITP has found that a lower dose of 100 mg weekly was effective[15]. Previous response to corticosteroids, secondary ITP and shorter duration of ITP, could be predictors of response to Rituximab[5].

Romiplostim and Eltrombopag are TPO - R agonists and increase the circulating platelet count by stimulation of platelet production by the bone marrow (BM) megakaryocytes[5,6,14]. Most studies include adults pacients with primary ITP, refractory to conventional treatment, only a few dates discuss the role of thrombopoietin receptor agonists in ITP associated with CLL [9,21]. Using Romiplostin was limited the use of steroids in severely immunocompromised patients; also was mentioned his usefulness for the determination of the histological diagnosis of the lymphoma through a safe and unmodified tissue sample biopsy [28].

Both TPO- R agonists have been associated with decreased bleeding events, reduced need for additional medications, and improved quality of life. The most important side effect are the rebound of thrombocytopenia upon abrupt drug discontinuation, the risk of BM reticulin formation and thromboembolic events [6,16]. Importantly, the cost/benefit balance should also be considered when using a TPO - R agonist[20].

Conclusions

Autoimmune thrombocytopenia is one of the cause of thrombocytopenia who can be associated with the malignant lymphoproliferative diseases. The perturbation of the immune response is a complex process , an important role have the auto-antibodies production against platelets and megakaryocytes. The diagnosis is more one of exclusion, and we have a lot of tests who help us for diferentions. About the therapy, it must take into account more parameters, not only platelets values: age, the risk of severe bleeding, the side effects of the treatement and the necessity of majore and / or urgency surgery. The lymphoma chemo-imunotherapy have a good response about autoimmune thrombocytopenia. Adding novel treatment is a true challenge if quality of life is not impaired.

References

1. Liebman HA. Recognizing and treating secondary immune thrombocytopenic purpura associated with lymphoproliferative disorders. *Semin Hematol.* **2009 Jan;46(1 Suppl 2):S33-6.**

2. Visco C., Ruggeri M., Evangelista M. L. Impact of immune thrombocytopenia on the clinical course of chronic lymphocytic leukemia. *Blood.* **2008 111: 1110-1116.**

3. Hauswirth A.W., Skrabs C., Schützinger C. et al. Autoimmune thrombocytopenia in non-Hodgkin's lymphomas. *Haematol.* **March 1, 2008; 93 (3): 447-450.**

4. Burghuber OC, Smolen J, Kühböck J. Immune thrombocytopenia in Hodgkin's disease. *Acta Med Austriaca.* **1986;13(2):55-9.**

5. Neunert. C.E. Current management of immune thrombocytopenia. *ASH Education Book.* **December 6, 2013; vol 2013 no. 1: 276-282.**

6.CukerA.andCinesD.B.ImmuneThrombocytopenia. **December 4, 2010; 2010 (1) : 377-384.**

7. Cines, D. B., Bussel, J. B., Liebman, H. A., & Luning Prak, E. T. (2009). The ITP syndrome: pathogenic and clinical diversity. *Blood,* **113(26), 6511–6521. doi:10.1182/blood-2009-01-129155.**

8. Johnsen Jill. Pathogenesis in immune thrombocytopenia: new insights. *ASH Education Book* **December 8, 2012 ; vol. 2012 (1) : 306-312.**

9. Hodgson K.,Ferrer G., .Moreno C. Chronic lymphocytic leukemia and autoimmunity: a systematic review. *Haematol.* **May 1, 2011; vol. 96 (5):752-761.**

10 . Kistanguri G and McCrae K. R. Immune Thrombocytopenia. *Hematol Oncol Clin North Am.* **Jun 2013; 27(3): 495–520.**

11. John W. Semple. Platelets & Thrombopoiesis. ITP has elevated BAFF expression. *Blood.* **December 17, 2009; 114 (26).**

12. Cines D. B, Liebman H., Stasi R. Pathobiology of secondary immune thrombocytopenia. *Semin Hematol.* **Jan 2009; 46 (Suppl 2) :S2-14**

13. Visco C. Rodeghiero F. Immune Thrombocytopenia in Lymphoproliferative Disorders. **2009 December; Volume 23(6): 1261–1274**

14. Provan D. Stasi R. Newland A.C. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood.* **January 14, 2010; 115 (2)**

15. Dearden C. Disease - Specific Complications of Chronic Lymphocytic. *Leukemia ASH Education Book* **January 1, 2008 vol. 2008 no. 1 450-1456.**

16. Advani R.H, . Zelenetz A. D, Abramson J. S. Non-Hodgkin's Lymphomas *J.Natl. Compr. Canc. Netw.* **2011;9:484-560.**

17. Maura F, MD, Visco C., Novella E. Biology and Pathophysiology, excluding Therapy: Poster II Immune Thrombocytopenia in Patients with Chronic Lymphocytic Leukemia Is Associated with Stereotyped B-Cell Receptors Blood *ASH Annual Meeting Abstracts* **2011.**

18. Moreno C., Hodgson K., Ferrer G. et al. Autoimmune cytopenia in chronic lymphocytic leukemia: prevalence, clinical associations, and prognostic significance. *Blood.* **December 2, 2010; 116 (23).**

19. Kalpadakis Christina. Autoimmune hemolytic anemia and autoimmune thrombocytopenia at diagnosis and during follow-up of Hodgkin lymphoma. Leukemia & lymphoma *Impact Factor. 2.61.* **01/2012; 53(8):1481-7. DOI: 10.3109/10428194.2012.660628 .**

20. Al-Nawakil C. Park S. Chapuis N. Salvage therapy of Autoimmune Thrombocytopenic Purpura revealing non-Hodgkin Lymphoma by the thrombopoietin receptor agonist romiplostim. *British Journal of Haematolog.* **January 2012; Vol. 156 (1): 145–147.**

21. Eltrombopag for the Treatment of Immune ThrombocytoPenia (ITP) Secondary to Chronic Lymphoproliferative Disorders (LPDs)**.** *ClinicalTrials.gov.* **Last review September 2012.**