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

Oprea Mădălina Marilena1, Ivănescu Ana-Maria1, Coliță A.1,2, Turbatu A.1, Coleș Elena2, Lupu Anca Roxana1,2

1 Hematology Department - Colțea Clinical Hospital, Bucharest
2 "Carol Davila" University of Medicine and Pharmacy, Bucharest

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 lead to thrombocytopenia. We should make a very rigorous 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 chemoinmunotherapy are the currently used treatment, individualized for each patient. The response to the lymphoma treatment is very good, and significant bleeding is rare.

Keywords: immune 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 lymphoproliferative diseases, but also may precede the diagnosis (in CLL flow citometry of older patients with ITP releved CD19/C5+ lymphocytes)[1,2].

Heterogenous histopathological 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 patients are: old age, advance disease and non-nodular sclerosing histology[1,4].

Ethio - pathogenesis

Immune thrombocytopenia is a complex disorder of immune disregulation which cause the autoantibody production[5, 6, 7]. The patient underlying condition could perturbed the immune system before the onset of ITP, but also a patient 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 pathophysiologcal 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 autoantibodies 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 monocyte 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
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, patients 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 obtain a complete remission of the lymphoid malignancy and not to treat the decreased platelet number[1]. Indication for treatment: platelets <20/30.000/mm³, active bleeding or high bleeding risk associated with platelets < 50.000/mm³[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 /mm³), minor or major surgery (<50/80.000 /mm³)[5, 6].

**Traditional first-line therapy of ITP** include corticosteroids, intravenous immunoglobuline (IVIG ) and immunoglobuline 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 IV Ig, 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 antiC-D20antibody is known to be active in both CLL and ITP, needs to be further investigated in ITP associated with CLL[2,5].

- 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 immunochemotherapeutic regimens used in NHL or in CLL: COP (Ciclofosfamida, Vin- cristin, 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 patients 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 patients 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 Romiplostim 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 treatment and the necessity of majore and/or urgency surgery. The lymphoma chemoinotherapy have a good response about autoimmune thrombocytopenia. Adding novel treatment is a true challenge if quality of life is not impaired.

References


