Thrombocytopenia in Chronic Hepatitis C

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Abstract: Hepatitis C is a disease caused by hepatitis C virus (HCV), which can cause liver cirrhosis and cancer. Chronic hepatitis C infection has extrahepatic manifestations, including thrombocytopenia. Patients with this disease have exhibited varied thrombocytopenia prevalence, with reported prevalence of more than 24%. Thrombocytopenia pathogenesis in chronic hepatitis C infection involves the interaction of various factors, including liver fibrosis, hypersplenism, bone marrow suppression, immune dysfunction and decreased levels and activity of thrombopoietin. Thrombocytopenia affects chronic hepatitis C infection treatment, including adjustment of antiviral dose especially Peg-IFN, delayed or canceled invasive procedures for diagnosis and therapy related to surgery. Thrombocytopenia therapy in patients with chronic hepatitis C can be divided into two: pharmacological treatments, including steroid administration, platelet transfusion, targeted thrombopoiesis therapy, thrombopoietin receptor activation therapy, and non-pharmacological therapy, including splenectomy and partial splenic embolization. Steroid administration for thrombocytopenia treatment in chronic hepatitis C infection is not used because it can worsen liver damage. Some pharmacological therapies still require further research and are still in the experimental stage in regard to their effectiveness and safety in thrombocytopenia treatment in chronic hepatitis C infection.

1 INTRODUCTION

Hepatitis C is a disease caused by hepatitis C virus (HCV), which can cause liver cirrhosis and cancer. An estimated 130 million to 170 million people worldwide (2-3% of the world's population) have hepatitis C virus infection. It is estimated that more than 350,000 death cases are associated with hepatitis C virus infection, mostly caused by liver cirrhosis and cancer (Averhoff et al., 2012). Chronic hepatitis C infection has extrahepatic manifestations, including thrombocytopenia. Thrombocytopenia is a condition characterized by a platelet count less than 150,000 cells/μL (Kasper LD, 2015). The thrombocytopenia definition varies among many reviewers and is based on platelet count. However, many definitions to explain thrombocytopenia depend on clinical relevance (Louie SK, 2011). The consequences of thrombocytopenia in chronic hepatitis C include complicated diagnosis (liver biopsy if necessary) and complicated treatment, and aggravate the clinical conditions in some diseases with hepatitis C virus infection, for example during surgery. Patients with chronic hepatitis C infection have a varied thrombocytopenia prevalence; for instance, most studies report a prevalence of more than 24% (Louie SK, 2011).

Another study reported that thrombocytopenia prevalence in the study population was 3% (51 of 1690 subjects), of which 1.2% were seronegative; 1.9% were HBsAg-positive; 5.2% were coinfected; and 10.2% were anti-HCV-positive (Wang et al., 2004). This study is a literature review that will address thrombocytopenia issues in chronic hepatitis C.

2 PLATELET LIFE CYCLE

Platelets are the smallest blood cells, which contain megakaryocyte cytoplasmic fragments. Megakaryocyte maturation involves nuclei duplication without cell separation, resulting in large cells. Megakaryocytes are found in the bone

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marrow, before moving to the sinusoidal wall and being released as large cytoplasmic fragments into the circulation. In its development, megakaryocyte cytoplasm is fragmented into platelets due to the blood circulation strength. Important regulators for megakaryocyte formation include IL-3, IL-6, IL-11, and steroid factor, in which thrombopoietin is the most dominant hormone. Platelets have a life cycle in the blood circulation of 10 days. The sequestration lien to platelets is estimated to be 1 compared 3 of the platelets present in the circulation. This fraction increases when splenomegaly is caused by increased portal venous pressure, but platelet lifespan does not change in this state (Maan et al., 2015).

3 THROMBOCYTOPENIA DIAGNOSIS IN CHRONIC HEPATITIS C

Thrombocytopenia pathogenesis in chronic hepatitis C is complex and involves the interaction of various factors, such as liver fibrosis or cirrhosis, hypersplenism, bone marrow suppression, immune dysfunction and decreased levels and activity of thrombopoietin (Fouad, 2013).

Thrombocytopenia in chronic hepatitis C infection is caused by three major pathological processes: decreased platelet production through central mechanisms of bone marrow suppression, platelet sequestration by the lien, and increased peripheral platelet destruction due to autoimmune mechanisms (Olariu et al., 2010).

3.1 Liver Fibrosis

The mechanisms causing thrombocytopenia in liver cirrhosis are platelet sequestration in the lien and decreased production of thrombopoietin in the liver (Hayashi et al., 2014). The prevalence and severity of thrombocytopenia is related to the severity of liver cell damage, as indicated by the increased fibrosis degree. The decline in platelet count occurs in liver fibrosis associated with progression, and a significant difference in platelet count is observed between stages, 182,000±47,500 cells/μL in patients with chronic hepatitis C, 85,900±33,600 cells/μL in patients with liver cirrhosis, and 66,700±25,200 cells/μL in liver cirrhosis patients with liver cancer (Osada et al., 2012).

3.2 Hypersplenism

Platelet destruction in peripheral or platelet sequestration is one of the major thrombocytopenia mechanisms in patients with chronic hepatitis C. Hypersplenism is a cause of peripheral platelet sequestration in patients with chronic HCV infection. Splenomegaly, with cirrhosis and portal hypertension, is significantly more common in thrombocytopenia patients than in subjects with a normal platelet count. Splenomegaly incidence is 10 times higher in thrombocytopenia patients (66%) than in patients without thrombocytopenia (6%). Moreover, based on multivariable analysis, splenomegaly is associated with the highest relative risk of thrombocytopenia. Previous studies have pointed out other causes of liver disease, and platelet sequestration due to lien enlargement is one of the major factors causing thrombocytopenia in patients with chronic hepatitis C infection (Zucker et al., 2012).

Splenomegaly is the most common cause of thrombocytopenia in chronic hepatitis C infection. Increased splenomegaly is associated with fibrosis stage progression. In 33 subjects with less than 100,000 platelets/μL , 25 had splenomegaly, while the rest did not suffer from splenomegaly (Osada et al., 2012).

3.3 Bone Marrow Suppression

Bone marrow suppression due to hepatitis C virus infection is a contributing factor of thrombocytopenia. Some patients with decreased RNA levels of hepatitis C virus after interferon therapy have a significantly increased platelet count in a state without hypersplenism or autoantibodies against platelets. Excessive alcohol consumption can have a direct toxic effect on megakaryocytes, resulting in ineffective production of platelets and thrombopoiesis (Fouad, 2013).

A study on subjects with severe thrombocytopenia found that most of them (93.34%) showed thrombocytopenia causes via peripheral and central mechanisms. In the subjects with moderate thrombocytopenia, 26.93% of them had bone marrow inhibition as a thrombocytopenia cause, 11.53% experienced autoimmune destruction as a thrombocytopenia cause, and most subjects (61.54%) showed both mechanisms. In subjects with mild thrombocytopenia, the most common thrombocytopenia cause is through peripheral mechanisms (Olariu et al., 2010).

3.4 Immune Dysfunction

In patients with chronic hepatitis C infection, autoantibodies against platelet surface antigens results in sequestration and destruction by macrophages in the lien and liver. It promotes hepatitis C virus bonding in platelets which can cause neoantigen formation on platelet surface or alteration of platelet membrane glycoprotein arrangement, resulting in autoantibody formation to fight target platelet glycoprotein (Weksler, 2007, Fouad, 2013). Platelet-associated anti glycoprotein (GP) antibodies is found in 64% of patients with chronic liver disease with a varied etiology. The formed immune complex and destruction by endothelial reticulum contribute to thrombocytopenia in patients with chronic hepatitis C virus infection. High titers of platelet-associated Immunoglobulin G-PAIgG show a complex immune process against platelets, which is present in 88% of patients with chronic hepatitis C virus infection. Levels of platelet-associated IgG (PAIgG) increase gradually along with an increasing degree of severity of liver disease (Weksler, 2007).

3.5 Decreased Activity and Thrombopoietin Level

Thrombopoietin is produced by hepatocytes, and is circulated with a constant release. Thrombopoietin stimulates all stages of platelet production, from megakaryocyte proliferation to platelet maturation and formation. At various stages of platelet production, circulating thrombopoietin performs its action in association with other hematopoietic cytokines, including interleukin-11 (IL-11), stainless factor, erythropoietin and stromal cell-derived factor-1. Thrombopoietin binds to platelets and stimulates platelet activation and function. Platelets not only bind to thrombopoietin but also degrade it; therefore blood thrombopoietin levels are normally regulated by total platelet mass. If decreased platelet production under normal conditions results in a decreased platelet count in the circulation that subsequently lowers thrombopoietin levels to bind platelets, it could increase plasma thrombopoietin concentrations. As a consequence, there is an increase in megakaryocyte formation to improve platelet homeostasis. This subsequently results in increased platelet production and release. As platelet count increases, excessive thrombopoietin is bound by platelets in the circulation, thereby thrombopoietin levels fall to normal levels (Weksler, 2007; Fouad, 2013). Patients with extensive liver cirrhosis have a decrease in hepatocyte function (with clinical manifestations of severe liver dysfunction), leading to decreased production of thrombopoietin. Therefore, the success of liver transplantation is found to increase plasma thrombopoietin levels followed by increased megakaryopoiesis that subsequently improves thrombocytopenia (Weksler, 2007).

3.6 Thrombocytopenia Treatment

Thrombocytopenia may be a negative effect of treatment with peg-interferon, which is given along with ribavirin, as a new treatment option for chronic hepatitis c infection. Interferon (IFN) therapy is known to cause a 27-37% decrease in platelet count. Pegylated interferon/ribavirin (PEG-IFN/RBV) combination therapy has more severe effects than non-pegylated interferon/ribavirin combination therapy. However, the most severe is PEG-IFN therapy as a monotherapy. The success of hepatitis C virus infection treatment is clearly demonstrated by the improvement of platelet count. Bone marrow suppression, including resistance to megakaryocytes formation, is believed to be a thrombocytopenia cause due to interferon treatment. Interferon treatment can suppress thrombopoietin secretion. As a consequence of thrombocytopenia during interferon therapy leading to interferon dose reduction, treatment of hepatitis C virus infection becomes unoptimized (Weksler, 2007; Fouad, 2013). Ribavirin therapy has a protective effect against decreased platelets due to interferon influence. This is demonstrated by a smaller decrease in platelet count in treatments using combination IFN-ribavirin therapy compared to interferon as a monotherapy (Weksler, 2007; Fouad, 2013).

4 THROMBOCYTOPENIA EFFECTS ON CHRONIC HEPATITIS C INFECTION TREATMENT

4.1 Adjustment of Antiviral Therapy Doses in Chronic HCV Infection

Current standard treatment of chronic hepatitis C infection still uses a combination of pegylated-interferon (Peg-IFN) with Ribavirin. However, therapy with Peg-IFN becomes problematic in patients with thrombocytopenia in both chronic

hepatitis C infection and liver cirrhosis. Thrombocytopenia will worsen during antiviral therapy with Peg-IFN; therefore, severe thrombocytopenia is generally considered to be contraindicated in Peg-IFN therapy. However, chronic hepatitis C treatment with DAA (Direct Acting Antiviral Agents) is currently available in some countries with minimal side-effects, particularly the absence of anemia and thrombocytopenia. A recent study on 61 patients with hepatitis C infection who were on the waiting list for liver transplantation were treated with a combination of sofosbuvir and ribavirin (RBV), resulting in an increase in platelet count during therapy with an average of 107,000/μL to 120,000/μL (Maan et al., 2015).

4.2 Delayed Invasive Procedure

Patients with chronic liver disease often require invasive procedures for diagnosis and therapy. The presence of thrombocytopenia may complicate this routine procedure, even leading to delayed or canceled invasive procedures. Currently, not all subjects can receive clinical guidelines to provide platelet transfusions in patients undergoing invasive procedures. In general, a platelet count of more than 80,000/μL is a requirement for clinicians to perform a percutaneous liver biopsy. However, some doctors have consider that a platelet count over 50,000/μL is safe for laparoscopy and transjugular liver biopsy. An analysis of Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial in 2,740 liver biopsies performed on patients with fibrosis and cirrhosis caused by chronic hepatitis C infection found 16 bleeding cases (0.6%). Bleeding is more common in patients with a platelet count of less than 60,000/μL. A study was conducted on 88 patients with terminal liver disease with cardiac catheterization planned, and 81 patients without liver disease as a control. This procedure is more difficult in patients with liver disease, as it causes 5.7% (5/88) of pseudoaneurysms compared with 0% in the control group. More severe hemorrhages occurred in the group with liver disease than in the control group (14.8% vs. 3.7%) (Maan et al., 2015).

5 MANAGEMENT

Not all patients with thrombocytopenia need treatment. There is no specific limit on platelet count in order to be treated, but thrombocytopenia therapy is more aimed at the patient's needs. Patients with symptomatic symptoms (bleeding, ptechie) due to thrombocytopenia require immediate platelet evaluation. Patients without symptomatic symptoms with a 50,000-150.000/μL platelet count are re-examined 1 to 4 weeks later, depending on the thrombocytopenia severity. A re-evaluation should be done immediately if the patient has symptomatic symptoms due to thrombocytopenia (Gauer and Braun, 2012).

Thrombocytopenia treatment caused by HCV depends on the eradication of HCV infection, resulting in improved thrombocytopenia. Interferon treatment continues but the dose is decreased if the platelet count decreases to less than 30,000/μL, or interferon therapy is discontinued if platelet count is less than 20,000/μL. The minimum effective dose of PEG-IFN is 1 g/KgBW/week. If platelet count remains less than 30,000/μL after lowering the dose to reach the minimum effective dose of PEG-IFN, supplemental therapy such as eltrombopag can be considered (Danish et al., 2010).

The therapeutic options of thrombocytopenia in chronic hepatitis C infection include:

1. Pharmacological Therapy

Steroids. Steroids are rarely used in the management of thrombocytopenia-related HCV infection. Various reports of steroid therapy may also result in an increased transaminase level and HCV viral load. Steroids can also increase bilirubin level which subsequently develops into jaundice (Fouad, 2013).

Platelet transfusion. A sufficient platelet count improvement is not always achieved as the patient may have serious complication risk related to transfusions of bacterial or viral transmission, refractory caused by alloimmunization, non-hemolytic febrile reactions, and expensive costs. Platelet transfusion complications occur in more than 30% of patients receiving platelet transfusions. The most common complication is the development of refractory conditions, which is believed to occur in 50% of patients receiving recurrent platelet transfusions. The refractory state arises from HLA alloimmunization, while non-immune platelet destruction is associated with splenomegaly, disseminated intravascular coagulation and septicemia.

The use of platelet transfusion as prophylaxis remains controversial. To date, there is still no consensus about the limit for platelet transfusion in patients with liver cirrhosis. Platelets have a shorter lifespan than red blood cells; therefore, if transfusions require repeated doses every 3-4 days as prophylaxis in patients with high risk of bleeding

complications, including surgical patients, infections and splenomegaly, the highest platelet transfusion is 50,000-100,000 cells/µL. Platelet transfusion is not a major indication in patients undergoing anti-HCV therapy, and is only given if the patient has active bleeding with a platelet count of less than 50,000 cells/µL (Fouad, 2013; Hayashi et al., 2014).

2. Factor Therapy with Target General Thrombopoiesis: Cytokines and Growth Factors

Thrombopoietin. Two types of recombinant thrombopoietin have been evaluated in clinical trials, namely recombinant human thrombopoietin (rhTPO) and pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF). Even though both may increase platelet counts in healthy experimental subjects and cancer patients, these clinical developments are stopped due to side-effects of thrombocytopenia and pancytopenia resulting from the emergence of a group of antibodies that neutralize thrombopoietin. However, the clinical development of this thrombopoietin study provides important clinical evidence of the principle of thrombopoietin agonist usage in the treatment of different types of thrombocytopenia (Weksler, 2007).

IL-11. In in-vitro studies, IL-11 works synergistically with other cytokines to stimulate various stages of megakaryocyte development. Megakaryocytes and their precursors express IL-11 receptors. IL-11 stimulates megakaryocyte maturation, platelet production and improvement of myelosuppressive hematopoietic systems. Clinically, the use of recombinant IL-11 (rhIL-11, oprelvekin) achieves success in specific patient groups. In tumor patients with severe thrombocytopenia due to myelosuppressive chemotherapy who have previously received a platelet transfusion, oprelvekin therapy gives positive results; therefore, oprelvekin administration is indicated for chemotherapy-related thrombocytopenia.

Side-effects associated with IL-11 include edema, fluid retention, arrhythmia and syncope. Adverse side-effects and platelet count improvement result in limiting the use of IL-11 based on the indication. A case study showed that oprelvekin may improve HCV-related thrombocytopenia; therefore, IL-11 could complement antiviral therapy for treatments in patients with HCV infection. However, oprelvekin has not been recognized for thrombocytopenia associated with chronic liver disease (Fouad, 2013). Platelet count and liver function improvement is found in most patients, but rhIL-11 treatment is stopped due to serious adverse incidence. The advantages of rhIL-11 therapy are believed to be only temporary (Fontana et al., 2008).

3. Therapy with Targeted Thrombopoietin Receptor Activation: Thrombopoietin Agonists

Eltrombopag, a non-peptide growth factor, is a selective thrombopoietin receptor agonist. In a phase 2, randomized double-blinded study, eltrombopag could facilitate platelet formation and maintenance in patients with chronic HCV infection-associated thrombocytopenia. Common side-effects during eltrombopag therapy include nausea, headaches and dry mouth, none of which require treatment discontinuation (Fouad, 2013). Another study found an increased platelet count after 10-day eltrombopag therapy at a dose of 50 mg/day. The dose was eventually reduced to 25 mg daily. Normal platelet counts were found for up to 3 months with continuous eltrombopag administration of 25 mg daily (Al-Jafar et al., 2014).

Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C-Related Liver Disease-1 (ENABLE-1) study found the average platelet count in 2 weeks after eltrombopag therapy in chronic hepatitis C infection patients who received antiviral therapy of 111,000 cells/µL, while ENABLE-2 study found 124,000 cells/µL and 89,500 cells/µL in a group receiving eltrombopag and a placebo, respectively. Therefore, platelet counts in patients receiving eltrombopag treatment in both ENABLE-1 and ENABLE-2 were higher than the placebo group during antiviral therapy (Burness, 2014).

Romiplostim is a thrombopoietin peptide agonist that binds to thrombopoietin receptors, stimulates thrombopoietin growth and megakaryocyte development, as well as increases megakaryocyte proliferation and maturation. In hepatitis C-associated chronic liver disease patients with severe secondary thrombocytopenia who will undergo surgery, romiplostim administration can increase platelet count to a level appropriate for surgery without bleeding episodes after surgery. Romiplostim is currently recognized by the FDA only for chronic ITP therapy in adults. It is administered once a week using subcutaneous injections at a dose of 1-10 mg/kg (Fouad, 2013; Hayashi et al., 2014; Maan et al., 2015).

Danazol. Danazol therapy is useful and provides good tolerance for treatment of refractory autoimmune thrombocytopenia with an unidentified mechanism. This therapy may activate antiplatelet antibodies and inhibit the mononuclear phagocytic system in patients with refractory thrombocytopenia. A recent study reported that platelet count increased

by more than 100,000 cells/μL in 10.6% of cases and 71% of platelet counts were maintained after danazol administration in hepatitis C infection-associated thrombocytopenia patients treated with Peg-IFN and ribavirin therapy (Fouad, 2013). Danazol therapy can maintain a stable platelet count or stop platelet decline. Patients receiving danazol therapy have a reduced risk of liver cancer. This therapy has mild side-effects, and reduces the relapse risk in patients who have a decreased Peg-IFN dose with danazol combination. Hepatitis C patients who received Peg-IFN, ribavirin and danazol combined therapy exhibited increased platelet and fibrinogen counts, decreased alanine aminotransferase and aspartate aminotransferase activities (Alvarez CG, 2014).

L-carnitine is a synthesized nutrient of lysine amino acids and methionine in human liver, brain and kidney. However, it is largely found in meat and milk. L-carnitine is a current adjuvant therapy to improve the condition of anemia, thrombocytopenia, leukopenia and immunological function. A recent study reported that L-carnitine in Peg-IFN-alpha administration with ribavirin could decreased platelet count during antiviral therapy. L-carnitine may affect platelet production and function through antioxidant mechanisms and arachidonic acid cascade inhibition. Arachidonic acid has a role in the process of blood platelet activation and free radical formation. Unlike arachidonic acid metabolism, L-carnitine has a direct effect on platelet activation and oxidative stress. L-carnitine inhibits the formation of superoxide platelet anions induced by arachidonic acid and collagen, but has no thrombin-associated platelet aggregation effects (Fouad, 2013). A greater decrease in platelet count is found in the Peg-IFN RBV combination therapy group compared to Peg-IFN RBV L-Carnitine combination. L-carnitine is currently recommended as a potential additional therapy to improve anemia, thrombocytopenia, leukopenia and immunological function (Malaguarnera et al., 2011).

4. Non-pharmacological Therapy

Splenectomy is used to improve thrombocytopenia in patients with hypersplenism. Even though some studies have reported successful treatment, splenectomy has the potential to have multiple complications, as it is an invasive procedure with a high-risk of bleeding in patients with portal hypertension, varicose veins and palpable spleen. Portal vein thrombosis and pancreatic duct leak require surgical management since they are splenectomy complications. Splenectomy also puts the patient at risk of overwhelming splenectomy sepsis syndrome (OPSS) (Fouad, 2013).

Splenectomy can be performed in certain patients with eligible platelet counts and no anti-HCV protocol. Low platelet counts are not an absolute contraindication for these patients. The surgery can be performed one week after interferon therapy discontinuation and with additional platelet transfusions. A patient had no severe bleeding and infection complication, both during and after surgery. After surgery, a rapid increase in platelet counts reached normal levels and were maintained at above 100,000/μL for one year after surgery (Huang X, 2015).

Partial splenic embolization (PSE) is a less invasive non-surgical, hypersplenism therapy than splenectomy. Catheter embolization is usually performed through the percutaneous femoral artery, as far as possible from the liver hilum to avoid pancreatic circulation. In some literature, PSE is reported as a successful thrombocytopenia therapy in patients with recurrent HCV infection undergoing treatment with interferon and ribavirin. In some patients, post-embolization syndrome occurs in the form of fever, upper left quadrant abdominal pain, pleural effusion, pneumonia and atelectasis. Abscesses and lupus ruptures are rare complications and are usually found in immunocompromised cirrhosis patients who have larger areas of embolization. These risks can be reduced by aseptic procedures, prophylactic antibiotics and pain control. PSE is a minimally invasive and effective procedure for thrombocytopenia caused by hypersplenism (Fouad, 2013).

Platelet counts before PSE range from 37,400-56,000/μL, and 80,000-240,700/μL two weeks after PSE. Likewise, leukocyte counts pre-PSE range from 2,300-4,200/μL, and increase to 4,000-12,600/μL after 2 weeks (Hadduck and McWilliams, 2014). Prior to PSE, platelet counts, hemoglobin level and leukocyte counts in a chronic hepatitis C-associated liver cirrhosis woman with recurrent episodes of vaginal bleeding for 2 months were 35,000/μL, 6.0 g/dL and 3,100/μL, respectively. PSE was conducted with strict aseptic techniques. After the PSE procedure, there was a 3-fold increase in platelet counts per day which continued to increase to more than 110,000/μL. The leukocyte count also increased from 3,000/μL to an average of 13,000/μL with stable hemoglobin at 11.0-13.0 g/dL (Hanafiah et al., 2013).

6 CONCLUSION

Chronic hepatitis C infection has extrahepatic manifestations, including thrombocytopenia. Thrombocytopenia affects chronic hepatitis C infection treatment, including adjustment of antiviral dose, especially Peg-IFN, delayed or canceled invasive procedures for diagnosis and therapy related to surgery. Not all patients with thrombocytopenia need treatment. There is no specific limit on platelet count, but thrombocytopenia therapy is more aimed at patients' needs. Thrombocytopenia therapy in patients with chronic hepatitis C can be divided into pharmacological treatments, and non-pharmacological therapy. Some pharmacological therapies still require further research and are still in the experimental stage regarding their effectiveness and safety in thrombocytopenia treatment in chronic hepatitis C infection.

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