Updates On Platelet Abnormalities in Chronic Liver Diseases

Essay
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List of Abbreviations

ADP	Adenosine diphosphate
APTT	Activated Partial Thromboplastin Time
APCR	Activated Protein C Resistence
BTG	Beta thromboglobulin
CAMP	Cyclic adenosine monophosphate
CLD	Chronic Liver Diseases
C-MPL	Myeloproliferative leukemia virus oncogen
DSRS	Distal Splenorenal Shunt
EHPVO	Extra Hepatic Portal Vein Obstruction
ERCP	Endoscopic Retrograde Cholangio-pancreatography
EST	Endoscopic Sclerotherapy
EVL	Endoscopic Variceal Ligation
GPIIb	Glycopeptide IIb

List of Abbreviations (Cont.)

GT	Glanzmann`s Thrombasthenia
IPH	Idiopathic Portal Hypertension
ITP	Idiopathic Thrombocytopenic Purpura
MYH-٩	Myosin Heavy Chain ٩
NCPF	Non Cirrhotic Portal Fibrosis
NCPH	Non Cirrhotic Portal Hypertension
OLT	Orthotopic Liver transplantation
PBC	Primary Billiary Cirrhosis
PF٤	Plasma factor ٤
PFA-١٠٠	Platelet Function Analyser
PG١٢	Prostaglandin I٢
PHT	Portal Hypertension
PVT	Portal Vein Thrombosis
TXA٢	Thromboxane A٢
TIPS	Trans Jagular Intrahepatic Porto systemic shunt

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THROMBOCYTOPENIA

Definition:

From a practical point of view, thrombocytopenia is defined as any decrease in platelet count below the lower normal limit (i.e. $<١٥٠\times١٠^{٩}$/L)However, it is often operatively considered as the level below which performing invasive manoeuvres (e.g. liver biopsy) or administering interferon therapy could be dangerous (i.e. $<٥٠–٧٥\times١٠^{٩}$ /L), or, lastly, as a threshold below which platelet transfusion is indicated (i.e. $<١٠\times١٠^{٩}$/L) **(Handin et al .,٢٠٠٤)**

As far as severity of disease is concerned, the prevalence of thrombocytopenia in patients with acute hepatitis is higher in those with liver failure when compared with those without liver failure (٥٢٪ vs. ١٦٪) **(Simon et al ., ٢٠٠٨).**

While among patients with CLD the prevalence of thrombocytopenia in acute hepatitis compared with chronic hepatitis patients (٦٤٪ vs. ٦٪) ,respectively. Lastly, in a large cohort of cirrhotic patients, we observed that 'any thrombocytopenia' has a prevalence of ٧٦٪, while ١٣٪ of the patients reach the 'liver biopsy or interferon (IFN) therapy' threshold, and ١٪ of the patients alone reach the 'transfusion trigger' threshold. Furthermore, the author observed that the

prevalence of the various degrees of thrombocytopenia in these patients was distributed differently depending on severity of cirrhosis, with an increasing trend in patients with more severe disease **(Giannini et al ., ٢٠٠٣).**

Thrombocytopenia perse is rarely a critical clinical problem in these patients, unless particular situations occur. Nevertheless, some studies identified thrombocytopenia as a parameter that is independently associated with the occurrence of complications of cirrhosis and patients' prognosis. Therefore, in well-defined and specific clinical settings, the availability of a tool that is able to safely increase platelet count in CLD patients would probably help the clinicians to manage their patients more appropriately **(Liangpunsakul et al., ٢٠٠٣).**

Thrombocytopenia in special situations

Thrombocytopenia can become a clinically relevant problem in particular situations. Well-defined clinical situations in which thrombocytopenia may become a significant clinical issue in CLD patients include: performing invasive diagnostic or therapeutic procedures, IFN treatment, bleeding oesophageal varices, management of patients on orthotopic liver transplantation (OLT) waiting lists, chemotherapy for solid tumours or haematological malignancies, and surgery. As far as

chemotherapy is concerned, patients with liver disease may experience more severe degrees of thrombocytopenia because of both treatment-induced myelosuppression and to the possible decrease in thrombopoietin (TPO) liver production caused by the hepatic toxicity of some treatment regimens. Transcatheter arterial chemo-embolization is increasingly being used in the treatment of cirrhotic patients with hepatocellular carcinoma, and the presence of thrombocytopenia can be a criteria for exclusion from treatment because of both the invasive nature of the technique and the concomitant use of one or more chemotherapeutic drugs. Furthermore, thrombocytopenia can be an important obstacle to surgical procedures or even simply to dental extraction. Although platelet transfusion is considered the 'golden standard' therapeutic option in all of these settings, patients can become refractory to platelet transfusion if they receive multiple transfusions over time. They may also have reactions to the transfusions, and they can be exposed to the risks of infections, especially when pooled products are administered **(Giannini , ٢٠٠٤).**

In cirrhotic patients, unequivocal features of advanced CLD are often present when the degree of thrombocytopenia is such that performing liver biopsy may be considered unsafe. Therefore, this should not be regarded as a limit, as histological

diagnosis would often be redundant in this setting. However, liver biopsy may be required in cirrhotic patients to diagnose hepatocellular carcinoma, and although current guidelines limit the role of liver biopsy in this situation **(Bruix et al ., ٢٠٠١).**

Recent studies have demonstrated that liver biopsy of focal liver lesions in these patients may reveal unexpected diagnoses **(Caturelli et al ., ٢٠٠٢)**

Furthermore, in the future, indications to liver biopsy in cirrhotic patients could paradoxically increase. In fact, liver biopsy can be used to evaluate particular histological features that may be useful for identifying patients at higher risk of developing hepatocellular carcinoma **(Borzio et al ., ٢٠٠٣).**

In this scenario, patients may also require repeated biopsies over time, thus increasing the likelihood of procedure-related adverse events. Thrombocytopenia can be an important limit to IFN therapy because of the fact that it is both an ineligibility criteria and a reason for treatment discontinuation **(Heathcote et al ., ٢٠٠٣).**

Therefore, it represents an important reason for denying or discontinuing treatment in patients who are most often in need

of anti-viral therapy. IFN administration is known to decrease platelet count because of a direct, dose-dependent effect on bone Marrow **(Schmid et al ., ٢٠٠٥).**

The use of new pegylated-IFN in patients with chronic viral hepatitis has led to an increase in terms of therapeutic efficacy, although side-effects have increased as well. Indeed, in one of the largest pegylated-IFN therapeutic trials, ٦٪ of the patients were excluded from treatment because of thrombocytopenia, and in the same study, thrombocytopenia was responsible for dose reduction and therapy discontinuation in approximately ٢٠٪ and ٣٪ of the patients ,respectively **(Heathcote et al ., ٢٠٠٠).**

These features are likely higher in every-day clinical practice. Interestingly, it has been shown that during IFN treatment of chronic viral hepatitis there is a blunted TPO response to the decreasing platelet count, which is more evident in cirrhotic patients **(Peck-Radosavljevic et al .,١٩٩٨).**

Noteworthy, successful IFN treatment is associated with restoration of the correct TPO platelet count feed-back mechanism, likely because of an improvement in liver function **(Chu et al .,٢٠٠٢).**

Lastly, patients awaiting OLT consistently have severe degrees of thrombocytopenia. These patients are subject to a greater risk of bleeding because of the high incidence of large oesophageal varices and coagulation impairment. Bleeding episodes may deteriorate liver function to the point of rendering the patient an unsuitable candidate for OLT, and may lead to patient death. Furthermore, treatment of bleeding episodes may require platelet transfusions, which can induce allo-immunization and refractoriness to new transfusions, and this may turn out to be an important issue when platelet transfusion is later needed to reduce the bleeding during OLT. Finally, recent studies have shown that anti-viral therapy may play a role in cirrhotic patients with chronic hepatitis C awaiting OLT, although in this setting thrombocytopenia once again was confirmed as a critical issue, as it caused treatment discontinuation in more than half of the patients **(Crippin et al ., ٢٠٠٢).**

THE ROLE OF THROMBOPOIETIN

The occurrence of thrombocytopenia in patients with CLD can be considered an event with multiple aetiologies. Indeed, thrombocytopenia may be caused by various factors which are

not mutually exclusive but, on the contrary, can act simultaneously **(Peck-Radosavljevic , ٢٠٠٠).**

While the original theory by Aster suggested that thrombocytopenia is exclusively attributable to increased pooling of platelets in the enlarged spleen because of portal hypertension . Many other factors are currently believed to be responsible for decreasing the platelet count in patients with CLD. Thrombocytopenia depends upon the stage of CLD, although aetiology of liver disease may also play a role. Two types of mechanisms may act alone or synergistically with splenic sequestration, thus determining thrombocytopenia. One is a central mechanism, which involves either myelosuppression because of hepatitis viruses or the toxic effects of alcohol abuse on the bone marrow, while the second mechanism is peripheral and involves the presence of antibodies against platelets **(Pockros et al .,٢٠٠٢).**

However, while both corticosteroids and immunosuppressants seemed to obtain successful results when thrombocytopenia was caused by immune-mediated phenomena . Neither surgical nor non-surgical treatments aimed at relieving portal hypertension were effective in reducing thrombocytopenia **(Ierardi et al ., ٢٠٠٣).**

In fact, well-conducted studies reportedly showed that even transjugular intrahepatic portosystemic stent shunt was not able to reverse thrombocytopenia, although it did prove to be effective in reducing the porto-systemic pressure gradient **(Karasu et al ., ٢٠٠٠).**

Consumption coagulopathy is likely to play a minor role, if any, in determining thrombocytopenia in patients with compensated liver disease, while it can be responsible for decrease in platelet count observed in cirrhotic patients with sepsis or shock. More recently, the characterization of TPO and the results of studies aimed at evaluating TPO pathophysiology in patients with liver disease have revealed a new scenario regarding the possible mechanisms of thrombocytopenia in the course of CLD. Thrombopoietin has only been described recently,although its existence was postulated several years ago **(Sohma et al ., ١٩٩٤).**

TPO is a glycoprotein consisting of ٣٥٣ aminoacids and has a molecular weight of ٣٠ kDa. The TPO gene is located on chromosome ٣q٢٧. TPO structure can be divided into two domains, amino- and carboxy-terminal .The former domain binds to the c-Mpl receptor and shares remarkable homology

with erythropoietin (EPO). On the contrary, deletion of the carboxy-terminal domain does not affect the activity of the protein in vitro, although it does decrease its bioavailability after parenteral administration. TPO acts at all levels of megakaryocytopoiesis together with other cytokines, while it is the sole regulator of platelet production and steady state **(Kaushansky , ١٩٩٨).**

Following the description of this important thrombopoietic agent, researchers shifted their attention from initial studies aimed at evaluating the role of TPO in patients with haematologic disorders to studies aimed at evaluating the role of TPO in thrombocytopenia of liver disease **(Pavithran and Doval ,٢٠٠١)**

On the basis of studies carried out on TPO-knock out mice and based on evidence that TPO is almost exclusively produced by the liver in adults, the results of these studies convincingly demonstrated that the relatively low TPO serum levels observed in cirrhotic patients are mainly the result of the decreased hepatic production of this hormone **(Ishikawa et al .,٢٠٠٠).**

In fact, TPO is produced by the liver at a constant rate and is cleared from circulation upon binding to its receptor (c-Mpl)