The Egyptian Journal of Hospital Medicine (Oct. 2011) Vol., 45: 424 – 433

Neutropenia in chronic hepatitis C during Interferon and Ribavirin Therapy.

Saadia Farid, Hala Morad and Samya Sweilam.
Department Of Tropical Medicine , Hematology and Biochemistry.
National Hepatology and Tropical Medicine Research Institute.

Abstract

Background: Neutropenia is a condition characterized by an abnormally low number of a type of white blood cells called Neutrophils, up to 25 % of people who take pegylated interferon, ribavirin and an HCV protease inhibitor experience Neutropenia.

Aim of the work: The study will be intended to analyze neutrophil counts and associated conditions of the liver and spleen , platelet count, liver enzymes and infections, during Interferon and Ribavirin therapy.

Patients and methods: One hundred forty two patients with chronic hepatitis C virus infection, their age between (18-59) years, selected from the National Hepatology and Tropical Medicine Research Institute were included in this study, during Interferon and Ribavirin therapy.
All the patients were subjected to the following history, through clinical examination, abdominal ultrasonography and collection of blood samples for routine investigations, CBCs and serological assay for ALT, Bilirubin.

Resuls: Our results revealed presence of 32.4 % anaemia, 18.3 % Thrombocytopenia, 16.9 % elevated ALT, 2.8 % elevated bilirubine, 16.9 % coarse liver, 25.4 % hepatomegaly, 16.2 % splenomegaly, and 16.9 % of cases complained different shapes of infection, associated with Neutropenia in patients of chronic hepatitis C during interferon and ribavirin therapy.

Conclusion: Our study concluded that the prevalence of Neutropenia in chronic hepatitis C virus infection patients 23.8 % during interferon and ribavirin therapy but it is not usually associated with infection.

Recommendations: Neutropenia is a complicated process that requires expert guidance from a medical provider.

Key Words: Neutropenia, chronic hepatitis C, side effect of interferon and ribavirin therapy.

Introduction

Many patients with chronic hepatitis C (HCV) infection undergoing treatment with pegylated interferon-alpha (PEG-IFN-alpha) and ribavirin develop neutropenia requiring dose reduction or granulocyte colony-stimulating factor (G-CSF) supp (Koirala, et al 2007). Hematologic side effects are common during treatment with pegylated interferon and ribavirin (Nachnani et al, 2009).
To meet normal physiologic needs, a healthy adult produces roughly 60 billion neutrophils each day. While neutrophils are produced by the bone marrow at a prodigious rate, their blood halph-life is short, 8 hours in a normal individual-Hence, lifespan vastly outnumber neutrophils by a ratio of about one thousand to one in the peripheral blood (Bolyard, et al., 2010).Under normal physiologic conditions, as stable equilibrium exists between marrow neutrophil production and peripheral utilization. When the production of neutrophils by the bone marrow is outspaced by utilization in periphery, the number of circulating neutrophils in the peripheral blood decreases and Neutropenia results (Bolyard, et al.,2010).
A common side effect of interferon alpha therapy is bone marrow suppression and particulary a reduction in white blood cell counts. Absolute neutrophil and lymphocyte counts typically decrease by 30 % to 50 % of baseline during therapy with the doses of interferon required to treat hepatitis C (Wongs, et al., 1996).
Neutrophil counts can fall to levels that are

associated with an increase in risk of bacterial infections and sepsis, in the large randomized controlled trials of pegylated or standard interferon combined with ribavirin neutropenia was listed as the most common reason for dose reduction (18 % of patients) and was a reason for early drug discontinuation in 1 % of patients (Manns, et al., 2010).

Neutropenia was defined as a peripheral absolute neutrophil count below 1,500 cells /ul, during therapy (Soza, et al., 2002). Patients with sever neutrpenia, and particularly those with neutrophils levels less than 0.2 x 109 / L, have a significantly increased risk of infection due to invasion of asurface bacteria in the mouth, intestinal tract or skin. Such patients frequently demonstrate

mucosal inflammation, particularly of the gingival and perirectal areas and often manifest cellulites, abcess, furunculosis, pneumonia or septicemia (Bolyard, et al.,2010)

Patients and Methods

One hundred forty two patients with chronic hepatitis C virus infection, their age between (18-59) years, selected from the National Hepatology and Tropical Medicine Research Institute were included in this study, during Interferon and Ribavirin therapy.

All patients have anti-HCV antibodies, HCV RNA in serum, evidence of chronic hepatitis on liver biopsy, elevated levels of aminotransferase above the upper limit, serum albumin, bilirubine, and prothombine time within normal limit with negative history of drug abuse, non reactive HBsAg, with exclusion of other chronic disease and pregnancy no clinical signs of decompensated liver disease. All the patients were subjected to the following history and through clinical examination, abdominal ultrasonography and collection of blood samples. A 5 ml whole blood was obtained by venipuncture plus edeta samples were analysed at Celltac F Automated Haematology analyzer, M E K-8222 J / K ,Japan Giza Medical.

Ethical consideration:

Informed consent was obtained from each patient at the time of drawing blood . The Research Ethical Committee of the General Organization for Teaching Hospitals and Institutes approved the study protocol.

Statistical analysis : Analysis of data was done by IBM computer using SPSS (Statistical program for social scienceversion 12). Data were expressed as description of qualitative valuable as numbers and percentage.

Results

The study included 142 patients of chronic hepatitis C virus infection with Neutropenia during interferon and ribavirin therapy.

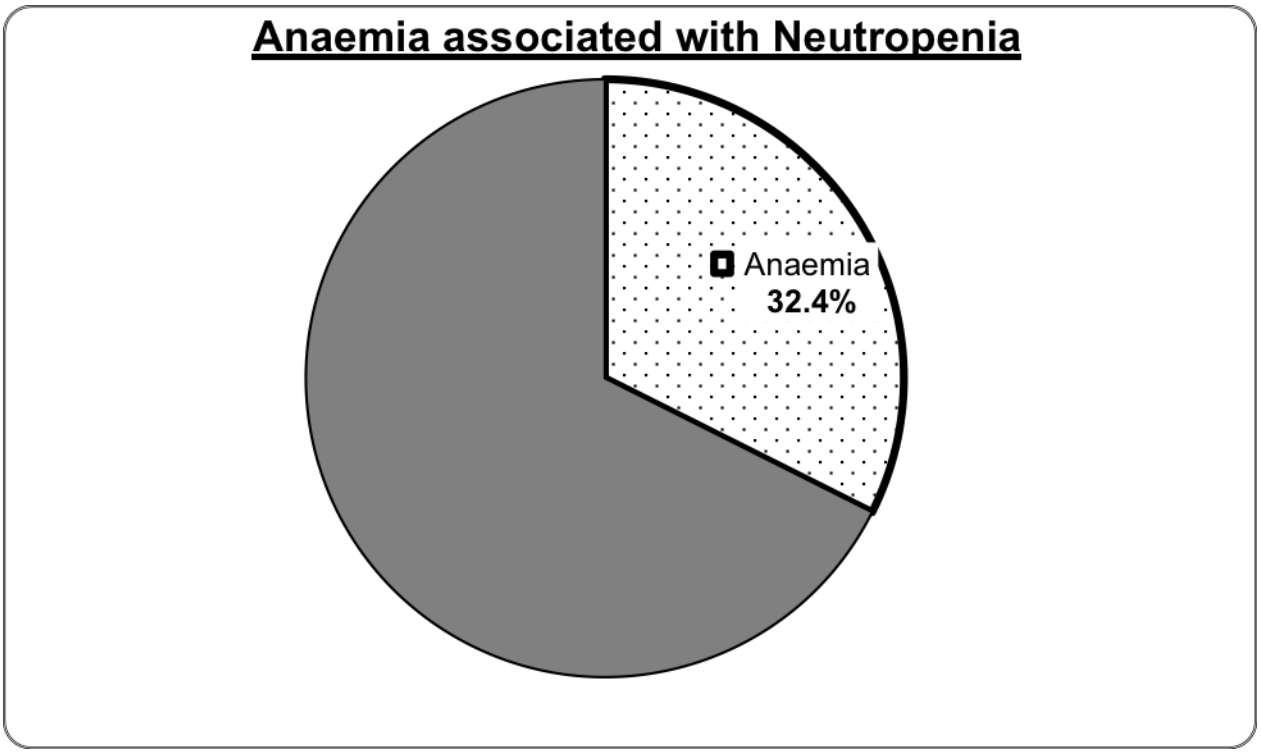
We found that: neutropenia was associated with:

* anaemia in 46 patients (32.4 %) during treatment (Graph 1).
*16.9 % (24 patients) with cirrhosis (Graph 2).
*25 % (36 patients) with hepatomegaly (Graph 3).
*16.2 % (23 patients) with splenomegaly (Graph 4).
*18 % (26 patients) with thrombocytopenia (Graph 5).
*17 % (24 patients) with ALT elevation (Graph 6).
*2.8 % (4 patients) with bilirubin elevation (Graph 7).
*16.9 % (24 patients) with infection (Graph 8).
*23.8 % the prevalence of neutropenia in CHCV infection (Graph 9).

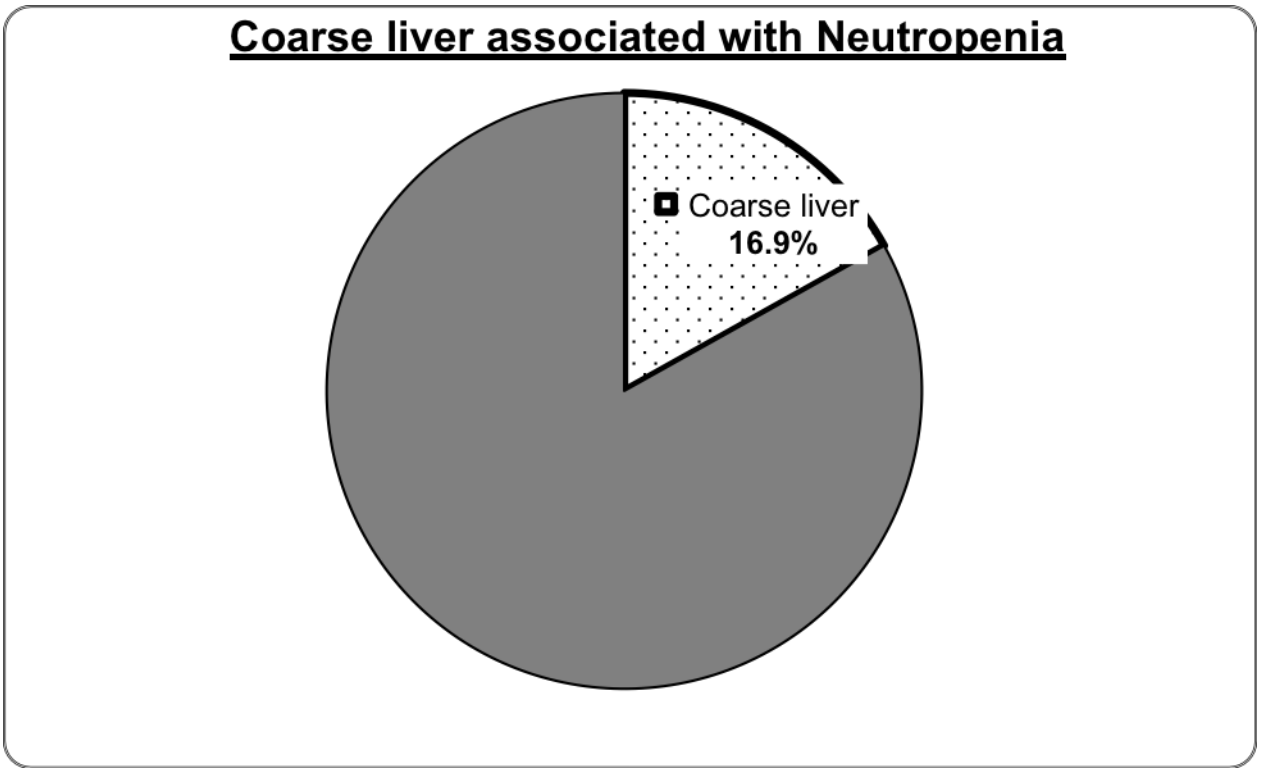
CBCs before Interferon and Ribavirin were within normal limit.

CBCs during Interferon and Ribavirin Therapy :

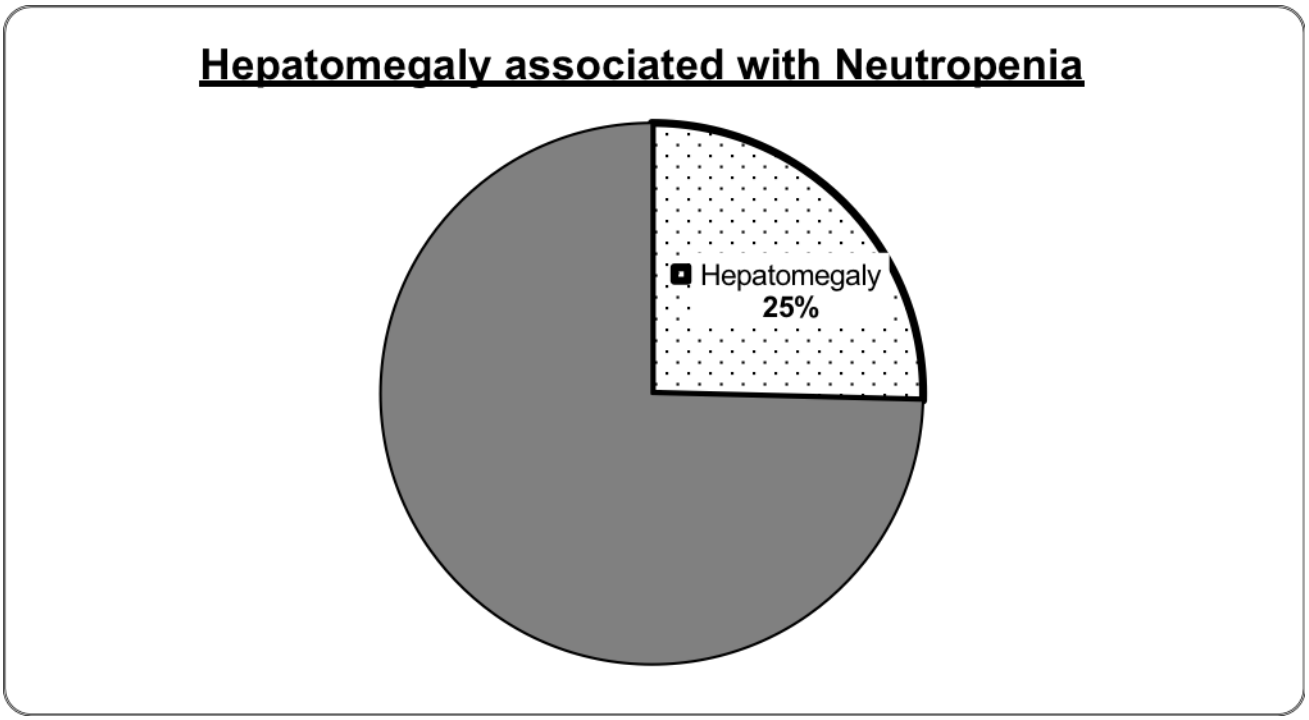
Test (CBCs)	Hb	Platelet	WBCs	Neutrophils
Lab. Abnormality	8 – 10.9 g / dl	50.000-100.000/cmm	1.6000-2.9000 /cmm	500-1000 /cmm
	RBCs count: 2.9-5.1 Millions/cmm		Differential Leucocytic count :	
			Neutrophis : 500- 1000 /cmm	
			Staff : 0 – 5 %	
			Segmented : 40 – 61 %	
			Lympocytes :20 – 59.2 %	
			Monocytes : 2-17 %	
			Eosinophils : 1-6 %	
			Basophils : 0-1 %	



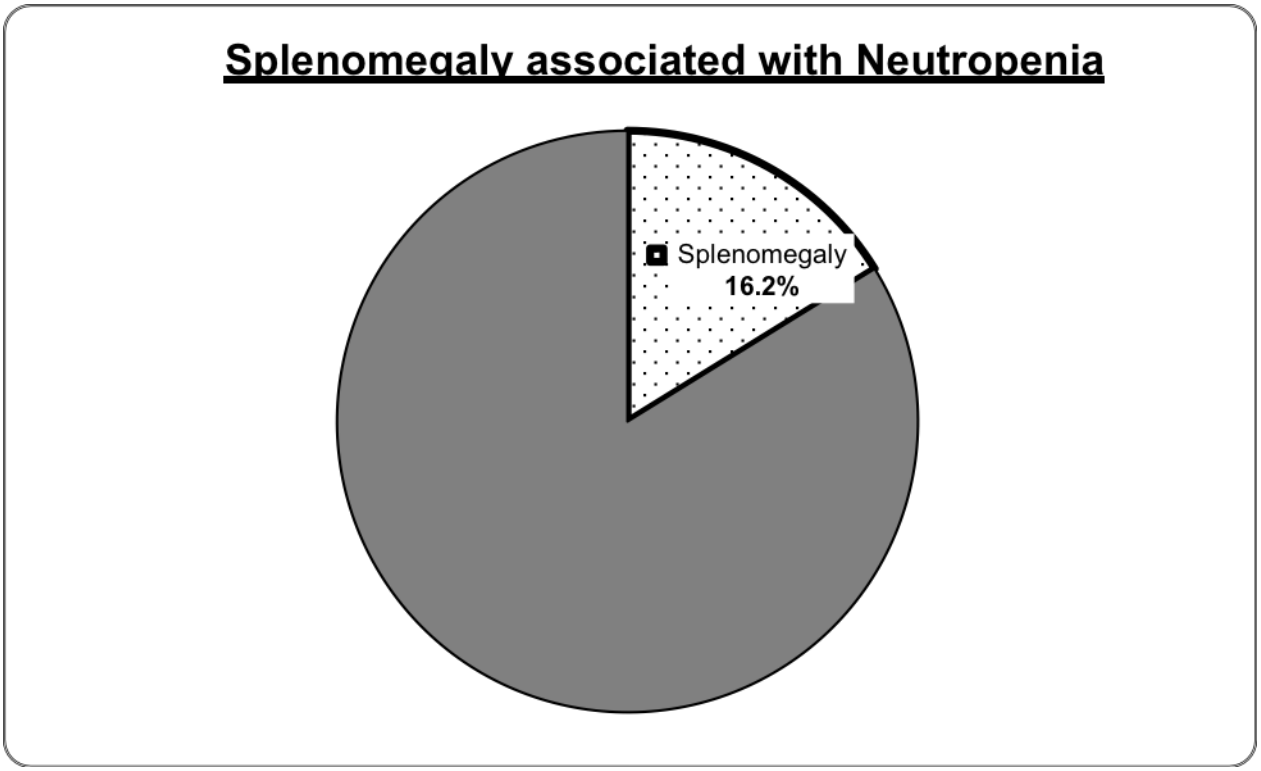
Graph (1): Illustrate the presence of 32.4 % anaemia in neutropenic CHCV patients during interferon and ribavirin therapy.



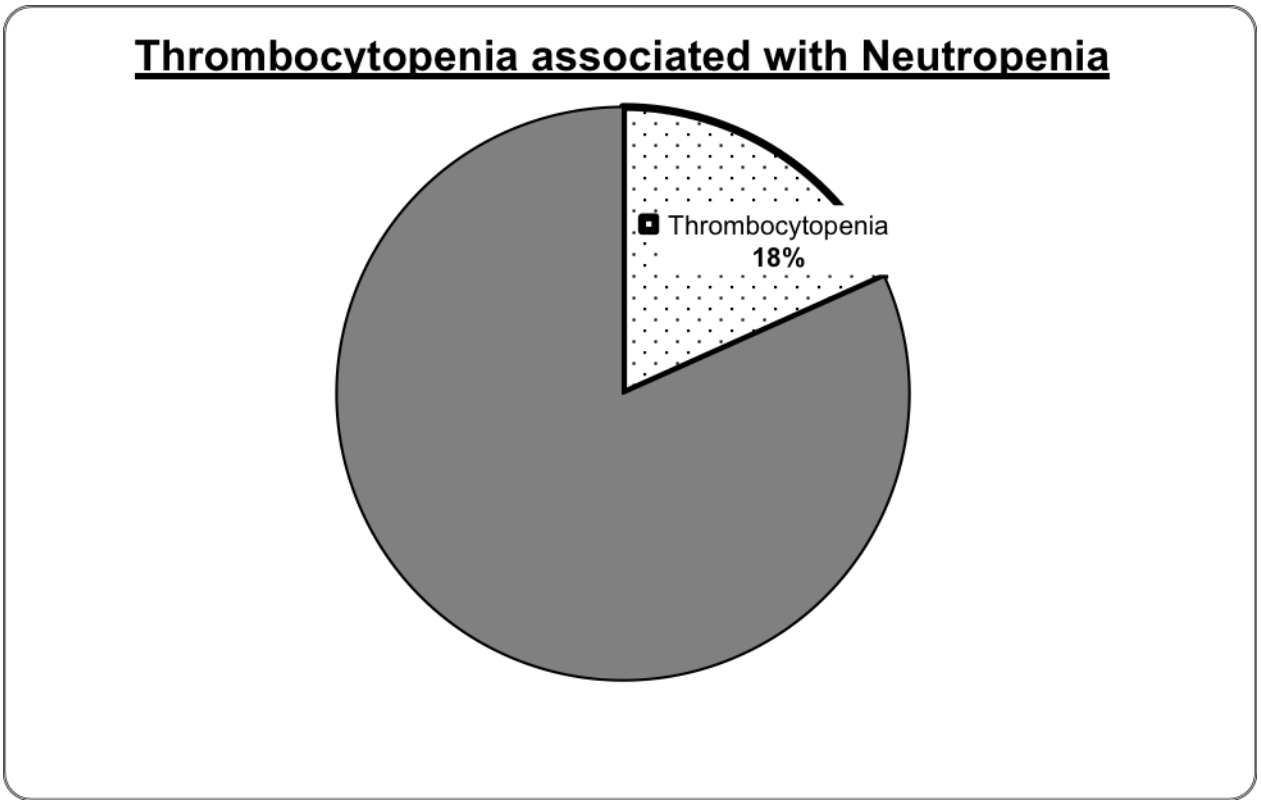
Graph (2): Illustrate the presence of 16.9 % liver cirrhosis in neutropenic CHCV patients during interferon and ribavirin therapy.



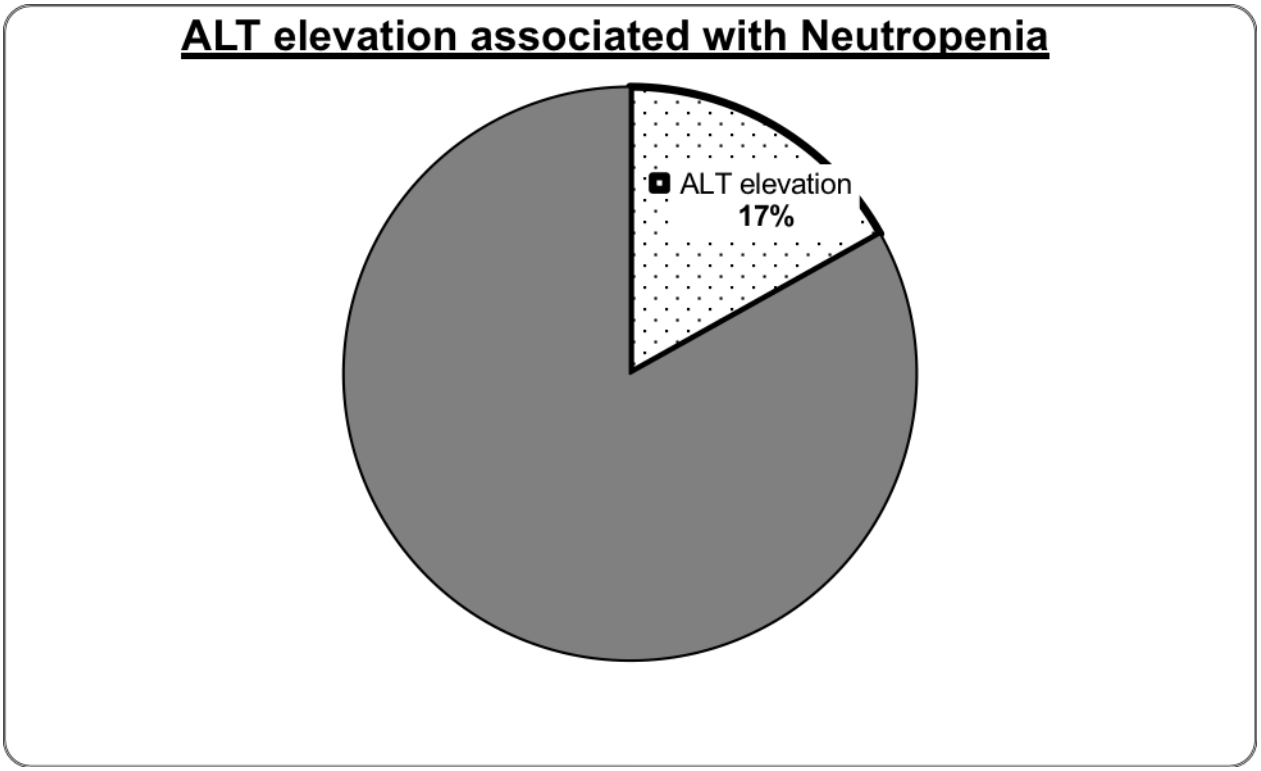
Graph (3): Illustrate the presence of 25 % hepatomegaly in neutropenic CHCV patients during interferon and ribavirin therapy.



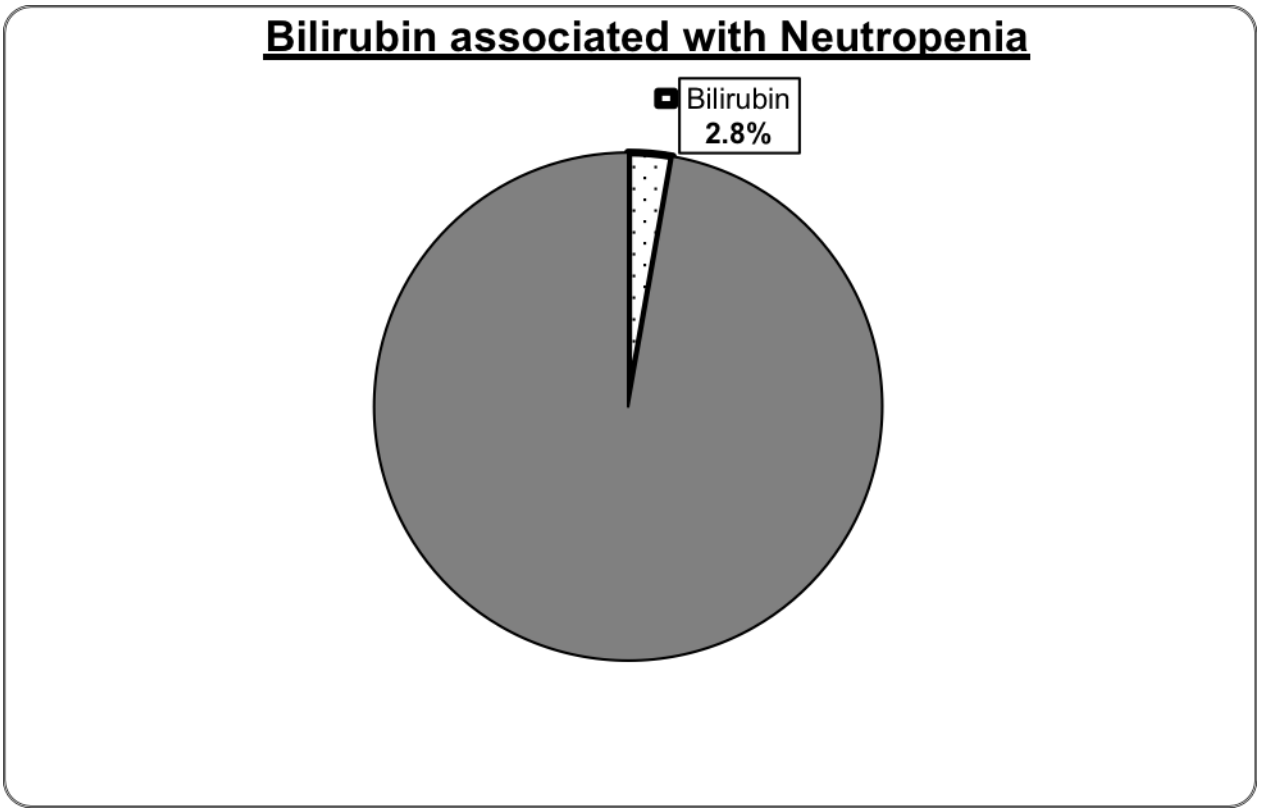
Graph (4) : Illustrate the presence of 16.2% splenomegaly in neutropenic CHCV patients during interferon and ribavirin therapy.



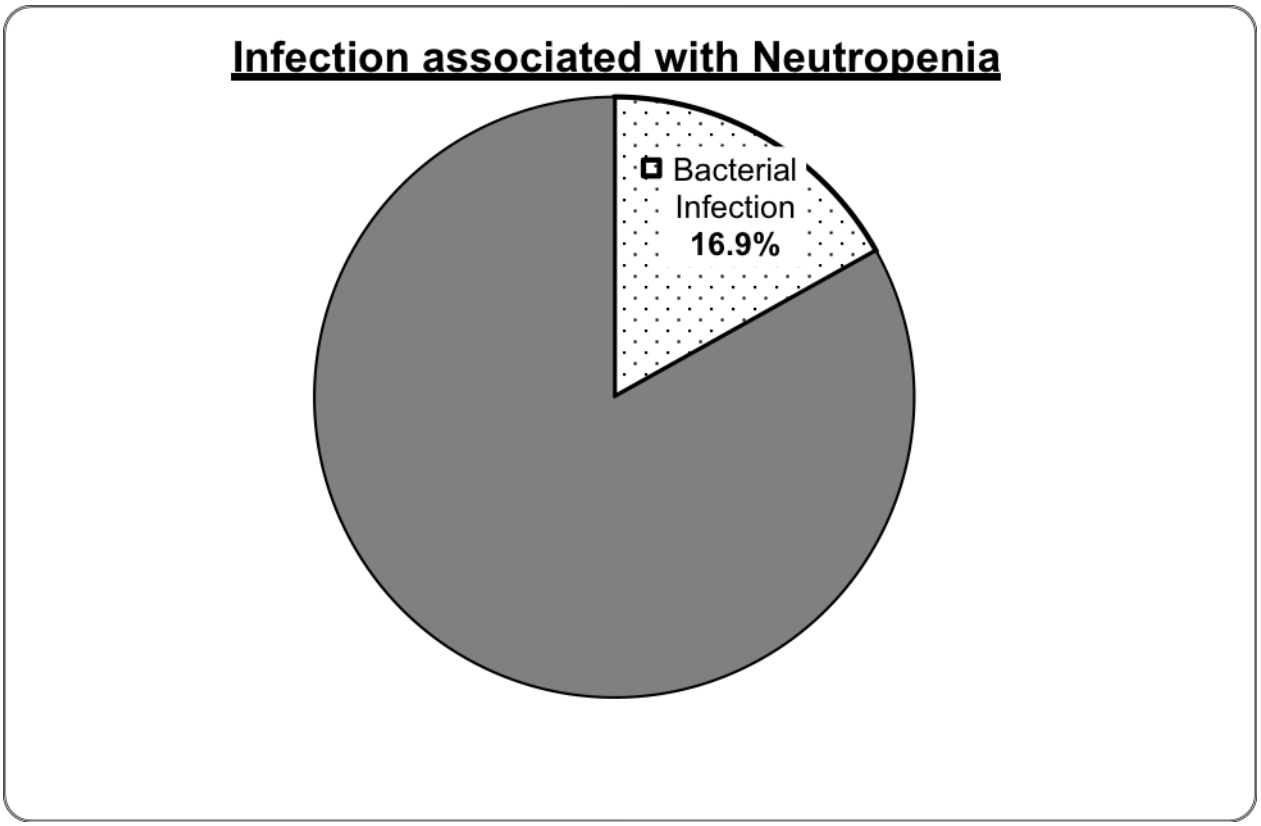
Graph (5): Illustrate the presence of 18 % thrompocytopenia in Neutropenic CHCV patients during interferon and ribavirin therapy.



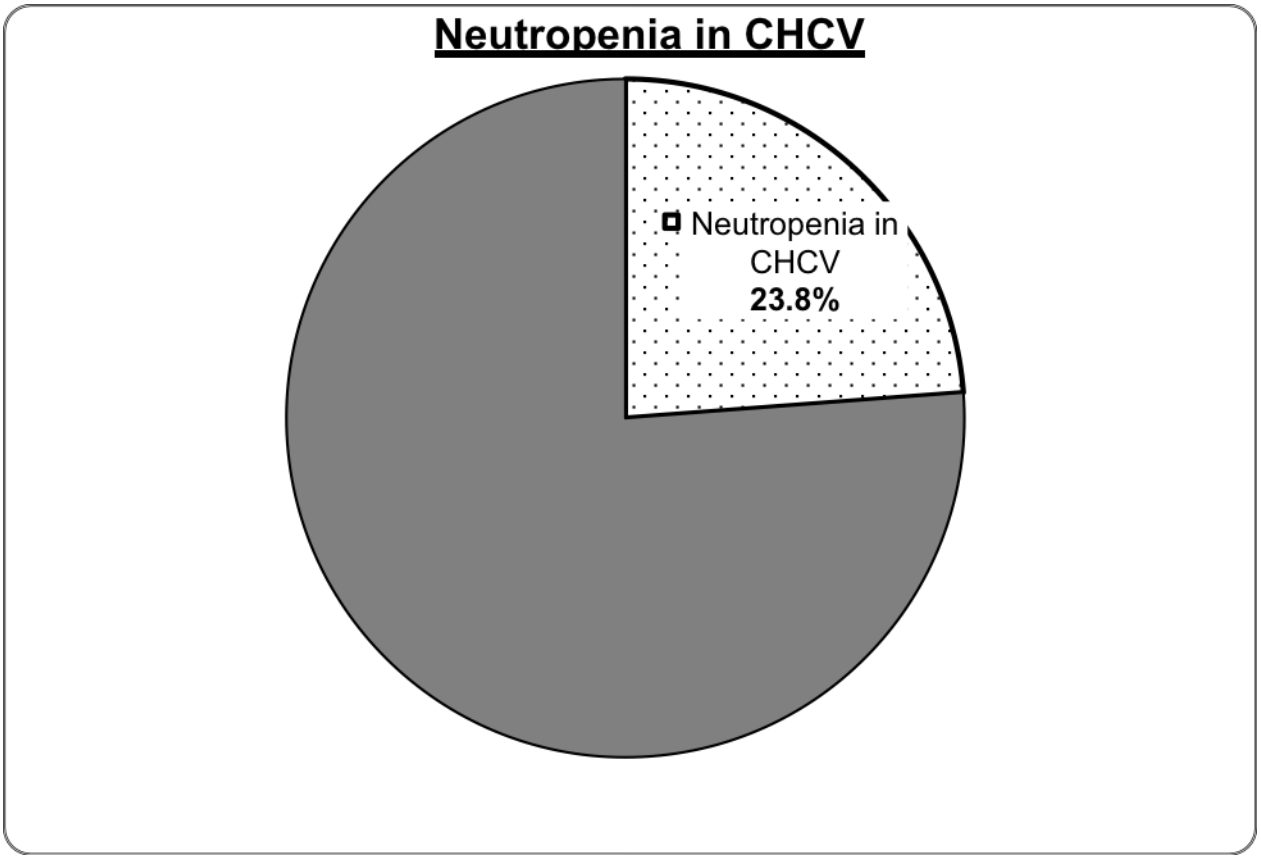
Graph (6): Illustrate the presence of 17 % ALT elevation in neutropenic CHCV patients during interferon and ribavirin and ribavirin therapy.



Graph (7): Illustrate the presence of 2.8 % bilirubin elevation in neutropenic CHCV patients during interferon and ribavirin therapy.



Graph (8): Illustrate the presence of 16.9 % bacterial infection in neutropenic CHCV patients during interferon and ribavirin therapy.



Graph (9): Illustrate the percentage ratio of neutropenia in CHCV patients during interferon and ribavirin therapy.

Discussion

In the large randomized trials of pegylated interferon combined with ribavirin neutropenia was lised as the common reason for dose reduction (18 %) of patients , and was a reason for early drug discontinuation in 1 % of patients (Manns, et al., (2001). Neutropenia was defined as a peripheral absolute neutrophil count below 1,500 cells/UL. During therapy, neutropenia was assessed at levels of 1,000, 750, and 500 cells /UL. The usual thresholds for dose reduction of interferon or discontinuation in therapy of hepatitis C { Soza, et al., (2002)}.

This work estimate neutrophil count by CBCs differential count examinations, and the associated factors, eg: anaemia (CBCs), liver cirrhosis, hepatomegaly and splenomegaly illustrated by ultrasound examination, thrombocytopenia (CBCs), ALT elevation, elevated bilirubin levels (serum), infections illustrated by culture and sensitivity or radiograph and clinical examination in chronic hepatitis C virus infection patients during pegylated interferon and ribavirin therapy.

In the present study, we found that the decrease in Hb % levels (anaemia) appear by frequent levels, associated with neutropenia during interferon therapy. { Kelleher, et al., (2010)} found that anaemia is extremely among patients taking PEG / RBV combination therapy for chronic hepatitis C and this finding in agreement with our results.

In our work, we observed by ultrasound examinations that liver cirrhosis was present by 16.9 % of the patients. Poynard, et al., (1997) & Poynard, et al., (2000) & Poynard, et al., (2001) postulated that chronic hepatitis C disease is generally slowely progressive : cirrhosis develops within 20 years in about 10-20 % of patients with chronic disease. {Shepard, et al., (2005)} found that 2-3 % of the world population are persistently infected with HCV, world wide up to 170 million individuals may be chronically infected, and are at risk of developing cirrhosis. Reherman and Nascimbeni, (2005) explained that fibrosis in chronic hepatitis C infection occurs as a result of the activation of hepatic stellate cells by cytokine and signaling

molecules induced by the inflammatory process. These produce and deposit extracellular matrix proteins then fibrosis begins around the portal tracts and gradually extends out into the lobules towards the central veins, factors shown to accelerate the progression to cirrhosis, include older age at HCV acquisition, male gender, and steatosis may lead to advancing fibrosis. Thein, et al., (2008) explained that a recent meta analysis examining stage specific transition probabilities suggested that the probability of transition to a higher stage of fibrosis is greatest between f 2 and f 3 (4 stage system);Metavir. This results correlated with our study, that the group included for interferon therapy (f 2 and f 3) after liver biopsy, and liver cirrhosis was present by 16.9 %.

European Pediatric hepatitis C virus Networks, (2005) demonstrate that in HCV infection 30 % develop chronic active infection with persistent viremia, frequent abnormal and in some cases, hepatomegaly likely indicating liver inflammation and an early stage HCV related liver damage. Deutsch ,(2010) observed that the physical examination of HCV patients may be normal or may demonstrate mild hepatomegaly or tendederness in advanced disease or cirrhosis the symptomatology and physical finding include hepatomegaly , splenomegaly, jaundice are more prominent and laboratory finding by significant for leucopenia. In the present study hepatomegaly associated with neutropenia in CHCV infection 25 % and this finding in agreement with our results.

Mistry and Jain (2011) postulated that chronic liver disease is usually accompanied "hyper splenism" diminished erythrocyte survival is frequent. In the present work splenomegaly in neutropenia in CHCV patients 16.2 % and this results correlated with our study.

Koirala, et al., (2007) found that hematological abnormalities including anaemia, thrombocytopenia and neutropenia are common adverse effects antiviral agents that are used to treat chronic HCV infection. In the present study we found that thrombocytopenia in neutropenia with CHCV infection 18 % and this results correlated with our results.

Cox, et al., (2005) discovered that serum aminotranferase decline from the peak values encountered in the acute phase of the hepatitis C disease, but typically remain abnormal by two fold to eight fold, serum ALT concentrations may fluctuate over time, and may even be intermittently or consistently normal. Serum aminotransferase levels remain abnormal after 12 months in 60 to 85 % of patients with C sporadic hepatitis. In the present work ALT elevation in neutropenia with CHCV infection patients during interferon and ribavirin therapy 17 % and this results in agreement with our results.

Fornari, et al., (1994) explained that all patients with hepatocellular disease show a variable degree of haemolysis. Chang , et al., (2005) observed that hepatitis C is associated with a higher incidence of gall bladder stones than patients with hepatitis B. Mistry and Jain, (2011) found that hepatocellular failure, and jaundice may affect the blood picture. Chronic liver disease is usually accompanied by "hypersplenism", diminished erythrocyte survival is frequent. In our work we found that 2.8 % of neutropenic CHCV patients have elevated bilirubin level during interferon and ribavirin therapy and this finding coincide with our results.

Franciscus, (2011) explained that the primary function of white blood cells is to fight off a variety of infections. There are many different types of white blood cells such as neutrophils. It is important to note that the vast majority of patients who develop interferon-induced neutropenia do not develop any serious infections that would be expected when compared to patients who develop neutropenia while on chemotherapy. In the present study, infection in neutrpenic patients during interferon and ribavirin therapy affected 16.9 % in the form of pharyngitis, gingivitis, otitis media, urinary tract infection, and cellulites and results correlated with our results.

Soza, et al., (2002) observed that neutropenia is frequent during treatment of hepatitis C with interferon and ribavirin but it is not usually associated with infection. Koirala, et al., (2007) found that after starting treatment with PEG-IFN-alpha, the absolute neutrophil counts (ANC) of 30 patients dropped below 1000 cells / ul after an average of 13 weeks, SD 10 weeks. Fraciscus (2011) postulated that clinical studies have shown that most people on HCV treatment experience some reduction in neutrophil count below the normal range, up to 20 % of people who take pegylated interferon and ribavirin experience neutropenia, up to 25 % of people who take pegylated interferon, ribavirin and an HCV protease inhibitor experience neutropenia. Wong, et al., (1996) who proved that a common side effect of interferon alfa therapy is bone marrow suppression and particularly a reduction in white blood cell counts. Absolute neutrophil and lymphocyte counts typically decrease by 30 % to 50 % baseline during therapy with the doses of interferon required to treat hepatitis C. In the present study neutropenia affected 23.8 % of CHCV

patients during interferon and ribavirin therapy and this finding in agreement with our results.

References

Franciscus A, (2011). Side Effect Mangement: Neutropenia. hcsp fact sheet. Hepatitis C Support Project. www. hc vadvo Cate.Org version 4. may.

Soza A, Everhart JE, Ghany MG, Doo E, Heller T, Promrat K, Park Y, Liang TJ, Hoofnagle JH, (2002). Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. Hepatology., 36:1273-1279.

Bolyard AA, Cottle T, Edards C, Kinsey S, Schwinzer B, Zeidler C, (2010). Types of severe Chronic Neutropenia-Neutropenia Support Association Inc. http//www.neutropenia.ca/about/types_of_neutropenia.html.

Chang TE S, Lo SK, Shyr HY, etalic (2005). Hepatitis C virus infection facilitates gallstone formation. J. Gastroenterol. Hepatol., 20: 1416-1421.

Cox AL, Netski DM, Mosbruger T, etalic (2005). Prospective evaluation of community acquired acute-phase hepatitis C virus infection. Cli. Infect.Dis., 40:951-958.

European Paediatric hepatitis C virus Networks (2005).Vertically acquired HCV: Natural history. Clinical infectious diseases., 41(1):45.www.uptodate.com/content/..hepatitis.c-virus/../35.

Fomari F, Imberti D, Squillante MM, etalic (1994). Incidence of gallstones in a population of patients with cirrhosis. J. Hepatol., 20: 797-801.

Koirala J, Gandotra SD, Rao S, Sangwan G, Mushtaq A, Htwe TH, Adamski A, Blessman D, Khardonri NM, (2007).Granulocyte Colony-Stimulating Factor dosing in pegylated interferon Alpha-Induced Neutropenia and its Impact on outcome of Anti-HCV Therapy. J. Viral Heplology., 14 :782-787.

Deutsch KF, (2010). Hepatitis C: the silent Epidemic. Clinical Advisor., January 22: http://www.clinicaladvisor.com/hepatitis-c-the-silent-epidemic/artic...

Manns MP, Hutchison MJG, Godon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, etalic (2001). Peginterferon alpha-2b plus ribvirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C : a randomized trial. Lanct., 358:958-965.

Nachnani JS, Rao GA, Bulchandani D, etalic (2009). Predictors of hematological abnormalties in patients with Chronic hepatitis C treated with interferon and ribavirin. Ann Hematol (Epub ahead of print).

Poynard T, Bedossa P, Opolon P, (1997). Natural history of liver fibrosis progression in patients with chronic hepatitis C. Lancet., 349: 825-832.

Poynard T, Ratziu V, Benmanov Y, etalic (2000). Fibrosis in patients with chronic hepatitis C: Dtection and significance. Sem.Liver Dis., 20: 47-55.

Poynard T, Ratziu V, Charlotte F, etalic (2001). Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. J.Hepatol., 34: 730-739.

Mistry PK, and Jain D, (2011). Haematological Disorders of the liver Sherlock's Disease of liver and Biliary system,12 th edition, chapter(4) p 48-69.

Shepard CW, Finelli L, Alter MJ, (2005). Global Epidemiology of hepatitis C virus infection. Lan. or Infectious Dis.,5: 558-567.

Rehermann B, and Nascimbeni M, (2005). Immunology of hepatitis Bvirus and hepatitis C virus infection. Nat. Rev. Immunol., 5: 215-229.

Kelleher TB, Afdhal NH, Bisceglie AM, and Travis AC, (2010). Management of treatment induced side effects for chronic hepatitis C. http : //www. Uptodate.Com/patients/content/topic.do?topic key=~E6IEIZXWxWxhv_6.

Thein H, Yi Q, Dore G, italic (2008). Estimation of stage-specific fibrosis progression rates in chronic hepatitis C infection: a meta-regession. Hepatology 48: 418-431.

Wong S, Kaita K, Gauthier T, Jones S, Minuk GY, (1996). A comparative trial of recombinant interferon alpha 2a versus alpha 2b on myelosuppression in healthy adult volunteers. Hepatogastroenterology 43: 301-305.

إنخفاض فى عدد كريات الدم البيضاء المتعادله فى مرضى الالتهاب الكبدى الوبائى سى المعالجين بعقار الانترفيرون و الريبافيرين

سعديه فريد قسم الامراض المتوطنه , هاله مراد قسم الهيماتولوجى , ساميه سويلم
قسم الكيمياء الحيويه بالمعهد القومى للكبد و الأمراض المتوظنه

الخلفيه: إنخفاض فى عدد كريات الدم البيضاء المتعادله (النبتروفيل) يصل إلى 25 % فى المرضى المعالجين بالانترفيرون + الريبافيرين و المعالجين بعقار البروتياز الرادع (إنهبيتور) فى مرضى الالتهاب الكبدى الوبائى سى .

الهدف من البحث : دراسه تحليليه لنسبة الإنخفاض فى عدد كريات الدم لبيضاء المتعادله (النيتروفيل) و يصحبها من تأثير بالنسبه (للكبد , الطحال , الصفائح الدمويه , الإنزيمات الكبديه" الانين , صفراء") .

طريقة البحث: شملت الدراسه عدد 142 من مرضى الالتهاب الكبدى الوبائى سى المزمن متوسط أعمارهم ما بين (59-18) عاما و العينات منتقاه من مرضى المعهد القومى للكبد و الأمراض المتوطنه , ويجرى جمع العينات خلال فترة تناول عقار الانترفبرون + الريبافيرين و جميع الحالات خضعت للفحوص الطبيه مع أخذ السيره الذاتيه للمرضى و عمل الموجات الصوتيه على البطن لجميع المرضى اللذين لديهم (أجسام مضاده للفيروس سى بالدم , بى سى أر رقمى , عينه كبديه تفيد الاصابه المزمنه بالفيروس) , مع وجود ارتفاع فى نسبة الامينوترانسفيراز فوق المستوى العادى بالدم و قد تم أخذ عينات الدم للمرضى لعمل الفحوصات الروتينيه السيرولوجى و صورة الدم الكامله .

النتائج : لقد أسفرت نتائج هذه الدراسه عن وجود إنخفاض فى عدد كريات الدم البيضاء التعادله (النيتروفيل) بنسبة 23.8 % , و يصاحب هذا الانخفاض وجود أنيميا فى الده (إنخفاض فى نسبة الهيموجلوبين بنسبة 32.4 % , معوجود تليف فى الكبد بنسبة 19.6 % ,و تضخم فى الكبد بنسبة 25.4 % , و تضخم فى الطحال بنسبة 16.2 % و إنخفاض فى الصفائح الدمويه بنسبة 18.3 % , إرتفاع فى إنزيم الالانين ترانسفيراز بنسبة 16.9 % , وجود إرتفاع فى نسبة الصفراء بنسبة 2.8 % , نسبة العدوى المصاحبه للنيتروفيليا تصل إلى نسبة 16.9 % .