Reactivation of hepatitis B virus in cancer patients receiving chemotherapy

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CERTIFICATE

This is to certify that **Dr. V.M. DURAI MAVALAVAN**. has been a D.M. Post Graduate Student between August 2008 and August 2011 in the Department of Medical Oncology, Madras Medical College.

This Dissertation titled **"Reactivation of Hepatitis B Virus in cancer patients receiving Chemotherapy"** is a bonafide work done by him during the study period and is being submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of the Branch VII D.M. – MEDICAL ONCOLOGY Examination.

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CONTENTS

INTRODUCTION

Nearly one third of the world's population have been infected with hepatitis B and the virus is endemic in many Asian countries. In India 4-4.75 per cent carry the virus.(1).

Hepatotrophic virus associated with acute and chronic hepatitis are

TABLE 1 -- The Hepatitis Viruses

Virus	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Type of virus	ssRNA	partially dsDNA	ssRNA	Circular defective ssRNA	ssRNA
Viral family	Hepatovirus; related to picornavirus	Hepadnavirus	Flaviridae	Subviral particle in Deltaviridae family	Calicivirus
Route of transmission	Fecal-oral (contaminated food or water)	Parenteral, sexual contract, perinatal	Parenteral; intranasal cocaine use is a risk factor	Parenteral	Fecal-oral
Mean incubation period	2–4 weeks	1–4 months	7–8 weeks	Same as HBV	4–5 weeks
Frequency of chronic liver disease	Never	10%	~80%	5% (coinfection); ≤70% for superinfection	Never

Virus	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Diagnosis	Detection of serum IgM antibodies	Detection of HBsAg or antibody to HBcAg	PCR for HCV RNA; 3rd-generation ELISA for antibody detection	Detection of IgM and IgG antibodies; HDV RNA serum; HDAg in liver	PCR for HEV RNA; detection of serum IgM and IgG antibodies

Hepatitis B , the cause of serum hepatits,is the most versatile of hepatotropic viruses.

HBV can produce

(1) Acute hepatitis

(2) Chronic non progressive hepatitis

(3) Progressive chronic disease ending in cirrhosis

(4) Fulminant hepatitis with massive liver necrosis

(5) An asymptomatic carrier state

HBV is present in the blood for the last stages of incubation period of 30-180 days and during the active episodes of acute and chronic hepetits and is present in all physiological and pathological body fluids with the exception of stools. HBV is a hardy virus and can withstand

extremes of temperature and humidity. Thus although blood and body fluids are the primary vehicles of transmission, virus may also spread by contact with body secretions such as semen, saliva, sweat, tears, breast milk and pathological effusions. Tansfusions, blood products, dialysis, needle stick accidents among the health care workers, intravenous drug abuse and sexual constitute the primary risk categories for HBV infection. In one third of the patient source of infection is unknown.

Outcomes of HBV infection:

Approximately 70% of the patients have mild or no symptoms and do not develop jaundice.the remaining 30% have constitutional symptoms such as anorexia , nausea, fever with jaundice and right upper quadrant pain. Almost all cases resolve spontaneously without treatment and is self limiting. Chronic disease rarely occurs in an adult in non endemic areas. Fulminant hepatitis is also rare about 0.5-1%.

HBV was first linked to hepatitis in the 1960s when Australia antigen (later known as HBV surface antigen) was identified.[25] The virus is a member of the *Hepadnaviridae*, a family of DNA viruses that cause hepatitis in multiple animal species. There are eight HBV genotypes with geographic distribution around the globe. The mature HBV virion is a 42-nm, spherical double-layered “Dane particle” that has an outer surface

envelope of protein, lipid, and carbohydrate enclosing an electron-dense, 28-nm, slightly hexagonal core. The genome of HBV is a partially double-stranded circular DNA molecule having 3200 nucleotides (Fig. 18-10). The HBV genome contains four open reading frames coding for:[26]

- A nucleocapsid “core” protein (HBcAg, hepatitis B core antigen) and a longer polypeptide transcript with a precore and core region, designated HBeAg (hepatitis B “e” antigen). The precore region directs the HBeAg polypeptide toward secretion into blood, whereas HBcAg remains in hepatocytes for the assembly of complete virions.

- Envelope glycoproteins (HBsAg, hepatitis B surface antigen), which consist of three related proteins: large HBsAg (containing Pre-S1, Pre-S2, and S), middle HBsAg (containing Pre-S2 and S), and small HBsAg (containing S only). Infected hepatocytes are capable of synthesizing and secreting massive quantities of noninfective surface protein (mainly small HBsAg).

- A polymerase (Pol) that exhibits both DNA polymerase activity and reverse transcriptase activity. Genomic replication occurs via an intermediate RNA template, through a unique replication cycle: DNA → RNA → DNA.

- HBx protein, which is necessary for virus replication and may act as a transcriptional transactivator of the viral genes and a wide variety of host genes. It has been implicated in the pathogenesis of liver cancer in HBV infection.

Clinical course of the infection:

natural course of the disease can be followed by serum markers (18-11).

- HBsAg appears before the onset of symptoms, peaks during overt disease, and then declines to undetectable levels in 3 to 6 months.

- Anti-HBs antibody does not rise until the acute disease is over and is usually not detectable for a few weeks to several months after the disappearance of HBsAg. Anti-HBs may persist for life, conferring protection; this is the basis for current vaccination strategies using noninfectious HBsAg.

- HBeAg, HBV-DNA, and DNA polymerase appear in serum soon after HBsAg, and all signify active viral replication. Persistence of HBeAg is an important indicator of continued viral replication, infectivity, and probable progression to chronic hepatitis. The appearance of anti-HBe antibodies implies that an acute infection has peaked and is on the wane.

- IgM anti-HBc becomes detectable in serum shortly before the onset of symptoms, concurrent with the onset of elevated serum aminotransferase levels (indicative of hepatocyte destruction). Over a period of months the IgM anti-HBc antibody is replaced by IgG anti-HBc. As in the case of anti-HAV, there is no direct assay for IgG anti-HBc, but its presence is inferred from decline of IgM anti-HBc in the face of rising levels of total anti-HBc.

With increasing life expectancy and the expected global increase in cancer, chemotherapy induced reactivation of hepatitis B is likely to

become an increasing problem.hepatitis B reactivation may occur in up to 50% of patients with lymphoma without prophylaxis and in up to 40% of breast cancer patients with positive serology.2. reactivation hepatitis may be fatal if it is not recognized and treated immediately. Preemptive treatment with Lamivudine is effective before chemotherapy for prophylaxis and treating active infection in some cases. Several risk factors have been proposed for reactivation of hepatitis B such as hematological malignancy, younger age, male gender and high pretherapy HBV-DNA levels.3. Patients with significant levels of hepatitis B virus (HBV) DNA in serum prior to chemotherapy and patients receiving intensive chemotherapy for hematological malignancies appear particularly more at risk.

Anthracyclines and steroids are among the chemotherapeutic agents most aften reported to be associated with reactivation of hepatitis. There are many chemotherapeutics that have been reported to cause reactivation hepatitis. Serum levels of aminotransferases,bilirubin , serological markers and HBV-DNA levels are important for hepatitis reactivation. Most patients who suffer reactivation of hepatitis B are positive for hepatitis B surface antigen (HBsAg) prior to chemotherapy and are therefore easily identifiable by routine screening. In addition,the very large population of patients who have been exposed to the virus and

have apparently cleared the virus as assessed by serological testing (HbsAg negative/hepatitis B core antibody [HBcAb] positive) may also be at risk of reactivation. These patients should be monitored and in some cases receive prophylaxis during chemotherapy.

Published experience with antiviral prophylaxis has largely been limited to the nucleoside analogue, lamivudine. The commencement of antiviral prophylaxis prior to chemotherapy and its continuation until restitution of normal host immunity is the cornerstone to effective prevention of hepatitis B reactivation. Though most of the studies are about hematological malignancies, there is much to be learned about solid tumors and hepatitis reactivation.

REVIEW OF LITERATURE

It is estimated that 2 billion people worldwide have been infected with the hepatitis B virus (HBV) and over 350 million are chronic carriers. The regional prevalence of chronic HBV varies widely. In areas of high endemicity in the Asia-Pacific region, it approaches 20%, whilst in south india the incidence of hepatitis B infection is about 4.5-5%.(1).

Patients who have been infected with HBV are vulnerable to disease reactivation during immunosuppressive pharmacotherapy. The clinical consequences vary from asymptomatic elevation of hepatic enzymes to severe hepatitis and death from fulminant hepatic failure. In addition to the direct harm caused by HBV reactivation, patient care may be compromised because of the need to delay or prematurely cease chemotherapy.(4)

Clinical significance of reactivation:

The likelihood of chronicity after acute hepatitis varies as a function of age. Infection at birth is associated with clinically silent acute infection but a 90% chance of chronic infection. Infection in young adulthood in immunocompetent persons is typically associated with clinically apparent acute infection but risk of chronicity of only

approximately 1%. Most cases of chronic hepatitis B among adults , however, occur in patients who never had a recognized episode of clinically apparent acute viral hepatitis.(5)

Degree of liver injury in patients with chronic hepatitis B is variable ranging from none in inactive carriers to mild to severe. Among adults with chronic hepatitis B, histologic features are of prognostic importance.(6). HBV reactivation can be asymptomatic.

In patients who have previously achieved immune control of HBV, immunosuppressive therapy may allow viral replication to escape, resulting in spread of infection within the liver and an increase in circulating HBV DNA. Following completion of immunosuppressive therapy, restoration of the host's immune response may lead to an immune clearance-like response that results in widespread cytotoxic T cell-mediated lysis of infected hepatocytes and severe liver injury. This syndrome of so-called ‘Hepatitis B reactivation following chemotherapy’ has been recognized.

Reactivation largely occurs in patients with chronic hepatitis B (CHB) who are positive for hepatitis B surface antigen (HBsAg), but it can also affect previously infected patients who have apparently cleared

the virus. These patients can be identified serologically by the presence of hepatitis B core antibody (HBcAb) in the absence of HbsAg.

Diagnosis:

Early studies of hepatitis B reactivation were hindered by a lack of uniformity in case definition and the relative insensitivity of previous methods used to measure viral replication. The current generally accepted definition of HBV reactivation, or a flare following chemotherapy, is the development of hepatitis with a serum ALT greater than three times the upper limit of normal, (2,3,7) or the occurrence of hepatitis during or immediately after cytotoxic chemotherapy, accompanied either by an increase in HBV-DNA levels of ≥10-fold, or an absolute increase that exceeds $9\log_{10}$copies/mL, in the absence of other systemic infections.(7,8) Thus, other than close monitoring before, during, and after chemotherapy, the sensitivity of the HBV DNA assays is crucial. The earlier branched DNA hybridization assay (Quantiplex HBV DNA assay; Chiron, Berkeley, CA) has a detection limit of 0.7×10^6 copies/mL, whereas recent polymerase chain reaction assays have a lower detection limit of 300 copies/mL.(9).

Clinical presentation:

The clinical presentation of HBV reactivation can range from asymptomatic anicteric elevation of hepatic enzymes to fulminant hepatitis. Icteric hepatitis is said to occur if the serum bilirubin is greater than twice the upper limit of the normal bilirubin concentration (□15 mmol/L). Typically, there is an increase in HBV DNA during or shortly after a cycle of chemotherapy which precedes any elevation of ALT by up to 3 weeks.(2) HBV reactivation may present as acute hepatitis with symptoms of malaise and fatigue; the average ALT elevation is 300 IU/L but may reach into the thousands. Serum bilirubin may range from mild to marked elevations.

Male patients with baseline ALT levels greater than 200 IU/L are three times more likely to develop a reactivation than patients with lower ALT levels. The HBcAb-IgM (the marker for acute hepatitis B) is present in about 60% of patients. Although hepatitis B viral DNA is expected to be present in high concentrations, it may be absent in 50% of patients at the time of peak ALT levels. Reactivation of chronic HBV infection may last weeks to months. A patient's underlying liver disease usually worsens during reactivation, and if cirrhosis is present, decompensation may occur with ascites, variceal bleeding, and liver failure in about 10% with mortality rates of 5%-10%.

Risk factors:

Virological factors:

Although hepatitis B e antigen (HBeAg) positivity in patients with cancer appears to be a risk factor(8,10,11) this has not been found to be universally the case. (12,13,14) .An increased risk has also been observed in the absence of HBeAg seropositivity, and this has been attributed to the presence of the precore/core promoter HBV mutants (*i.e.*, HBeAg-negative/hepatitis B e antigen–positive chronic hepatitis B infection).(15).This finding has also been associated with severe fulminant hepatitis.(12,13).

With sensitive assays such as real-time polymerase chain reaction, recent studies in patients undergoing conventional-dose and high-dose chemotherapy with HSCT have shown that high pre-chemotherapy HBV DNA load, defined as above 3×10^5 copies/mL, is associated with increased likelihood of developing reactivation.(16,17).

Cancer type and treatment factors:

Several anticancer immunosuppressive agents have been associated with HBV reactivation (Table 3); these could be broadly categorized into

conventional cytotoxic agents(18,19,20) and biologic response modifiers with anti-B and -T monoclonal antibody therapies.

Among the former, corticosteroids and anthracyclines have been most frequently associated with the condition(2,3,8,,21)HBV DNA contains a glucocorticoid responsive element that has been reported to facilitate HBV replication,(23,24) while anthracycline has been demonstrated *in vitro* to stimulate HBV DNA secretion from HepG2-derived 2.2.15 cells in a dose-dependent manner.(25).

Reactivation rates of 48% have been reported in HBsAg positive patients treated with chemotherapy for lymphoma, with an associated mortality of 4%.17 Other studies report an incidence of HBV reactivation following chemotherapy for lymphoma between 24 and 67% and a mortality of 4–41%.(2,8,21,26) In part this very high incidence may be explained by the intensive chemotherapy necessary for lymphoma, but also may be due to the relatively high prevalence of HBV infection observed in patients with this condition.(2,29,30,31) Patients receiving intensive cytoreductive therapy and high dose Chemotherapy prior to hematopoietic stem cell transplantation are also particularly susceptible to HBV reactivation, with rates approaching 50%.(32,33,34,35,36).The level of viral replication prior to chemotherapy appears the most

important risk factor for HBV recurrence in this group.(32) In patients receiving chemotherapy for non-hematological tumors, the highest rates of HBV reactivation have been reported in patients with breast cancer where the incidence ranges between 41 and 56%.(25,36) The rate of reactivation appears to be lower in patients treated for other solid tumors, ranging between 14 and 21% in different studies.(2,37,38)These differences are most likely due to the types of chemotherapy used for these conditions rather than the nature of the malignancy *per se*.

The recent introduction of therapeutic monoclonal antibodies against B and T lymphocytes such as rituximab (a chimeric mouse human monoclonal antibody against CD20+ malignant lymphoid cells) and alemtuzumab (a humanized monoclonal antibody against anti-CD52+ malignant lymphoid cells), used alone or in combination with cytotoxic therapy, has been associated with HBV reactivation.(39,40-43) In October 2004, the U.S. Food and Drug Administration reported a possible relationship between fulminant hepatitis and rituximab use. These agents have been found to induce profound and durable B and T cell depletion.(46,47)Although lysis of HBV-infected hepatocytes is mainly mediated by CD8+ cytotoxic T cell immunity, B cells may also act as antigen-presenting cells and prime cytotoxic T lymphocyte–specific responses in HBV infection.(48)The progressive B and T cell depletion

may also account for the increasing incidence of HBV reactivation in anti-HBs– and/or anti-HBc–positive patients undergoing chemotherapy with these agents . Among the 7 cases reported, 3 developed fatal hepatic failure despite lamivudine therapy, possibly related to the delay in antiviral administration, and another had persistent HBsAg positivity(45).

Reactivation of HbsAG negative and HBc antibody positive patients. In individuals with resolved HBV infection (*i.e.*, HBsAg-seronegative, anti-HBs–postive and/or hepatitis B core antibody [anti-HBc]–positive), HBV replication has been shown to persist in the liver and in peripheral blood mononuclear cells.(50,51) Two reports described patients receiving conventional dose chemotherapy. In 1 report,(49) 12 of 17 patients with hematological malignancies had dramatic reduction of anti-HBs titer, and 5 (30%) had evidence of seroreversion with reappearance of HBsAg—2 of whom had persistent HBsAg despite cessation of chemotherapy. The second report described 51 Chinese patients with lymphoma—9 of whom developed hepatitis, with 2 having raised HBV DNA during chemotherapy,resulting in a 4% HBV reactivation rate.(8) In both reports, hepatic impairment had been mild and no direct HBV-related mortality was observed.

Management of reactivation

Until recently, aggressive supportive therapy and discontinuation of cytotoxic chemotherapy has been the mainstay of treatment. Interferon, which has both antiviral and immunomodulatory functions, has been shown to control hepatitis during chemotherapy.(27)

However, the use of conventional interferon(83) may be limited by the possibility of fatal hepatitic flare via augmentation of the immunomediated destruction of hepatocytes. Lamivudine, a nucleoside analogue, has been shown to have substantial activity in chronic HBV infection.(53-58) Lamivudine has also been claimed to be effective in controlling viral replication during HBV reactivation(60,61)(82-84) thereby allowing individual patients to continue cytotoxic chemotherapy upon maintenance of a sufficient hepatic function.(60,62) Sustained HBeAg seroconversion and undetectable serum HBV DNA level for at least 3 months after the discontinuation of lamivudine therapy have also been observed in some patients who were initially HBeAg-seropositive,(62) and the postulated mechanism has been a high immune response to HBV reactivation that allows elimination of covalently closed circular DNA in hepatocytes in conjunction with suppression of viral replication.Lamivudine has also been reported to be effective in cases of

hepatic decompensation during HBV reactivation(52,61) and in cases that involve a precore HBV mutant.(62,60)

Prevention:

Lamivudine prophylaxis is an effective means of reducing the reactivation . many studies have proved the efficacy of the prophylactic lamivudine.(58-68). Most of the studies have favoured that lamivudine should be started prior to first dose of chemotherapy and should be continued atleast 6 months after chemotherapy , some studies have continued lamivudine for more that a year.

Inspite of prophylactic lamivudine, reactivation has been recorded in some of the studies.On the other hand, despite lamivudine, HBV-associated mortality has been reported in up to 20% of the HBsAg-positive patients treated(89). This has been postulated to be due to a delay in antiviral administration at a time when severe hepatic impairment with massive hepatic damage had already occurred One potential means of minimizing the risk of HBV reactivation is the avoidance of corticosteroid therapy as part of (85)chemotherapeutic/antiemetic regimes in HBsAg carriers., (69,70) However, HBV reactivation may still occur in association with the use of other cytotoxic/immunosuppressive agents.(71) Furthermore, this may lead to suboptimal therapy and may

even jeopardize the patient's chance of cure. In a prospective study of 50 patients with non-Hodgkin's lymphoma who were randomized to receive either the standard steroid- containing regimen; (85) (prednisolone /epirubicin/cyclophosphamide/etoposide) or a steroid-free regimen (epirubicin/cyclophosphamide/etoposide), whereas the cumulative incidence of HBV reactivation was significantly higher in the steroid-containing study arm (73% vs. 38%; *P* = .03), patients in the steroid-free arm had a significantly lower rate of complete remission and shorter overall survival.(71) (88).

Leaw et al(72) reported that interferon administered from the start of chemotherapy prevented HBV reactivation in 13 lymphoma patients. However, using interferon-containing combination chemotherapy for patients with inoperable HBV-related hepatocellular carcinoma has not reduced the incidence of HBV reactivation.

Reviewing the literatures, incidence of reactivation of Hepatitis B virus is varying according to malignacy and the chemotherapy schedules.

In one of the study at Dept of medical oncology at SELUCK University at Turkey,(74) retrospectic study, retrospectively examined about 1826 patients 95 patients were found to be Hepatitis B surface antigen positive,59 patients were eligible for the final analysis, 9 patients

had reactivation. They included 50 patients with solid malignancy and 9 patients with hematological malignancy. All the patients were not on Lamivudine prophylaxis. Among the 9 patients who underwent reactivation lung cancer 3 patients, breast 2 patients , GIT malignancy 3, and Lymphoma 1 patient. All the patients received standard chemotherapy schedules with or without radiotherapy as per regimens.

In another study by Dr.Yeo et.al. (75) at dept clinical oncology at Chinese University of Hong Kong- studied the reactivation of hepatitis b virus among the breast cancer patients receiving chemotherapy. It was a prospective study.

The main objectives were to determine the incidence of HBV reactivation in breast cancer patients undergoing conventional chemotherapy; to investigate whether "serial HBV DNA monitoring" improves the accuracy of diagnosing HBV reactivation when compared with previous schema that only measured HBV DNA at the time of clinical hepatitis ("conventional monitoring"); and to assess the clinical consequences as a result of developing the condition. The secondary objective was to identify risk factors associated with this condition. Over an 18-month period, 41 patients were studied. Ten developed HBV reactivation by conventional monitoring criteria, but with serial HBV

DNA monitoring, seven additional patients were diagnosed when increased HBV DNA levels were detected before, but not concomitant with, clinical hepatitis. Thus, a total of 17 patients (41%) developed HBV reactivation. Premature termination of chemotherapy or delay in treatment schedules occurred in 71% of the patients who developed viral reactivation, as compared with 33% in those who did not develop the condition (P = 0.019). No risk factors associated with the development of HBV reactivation could be identified. Serial monitoring of HBV DNA, in addition to liver function,increases the sensitivity of diagnosing of HBV reactivation.

In another study by Dr.YEO. et al at dept of clinical oncology Hong Kong, about the reactivation of Hepatitis B virus in Hepatocellular Carcinoma patients underwent chemotherapy.The prospective study was conducted to determine the incidence of HBV reactivation, the associated morbidity and mortality, and possible risk factors. About 102 HBsAg-positive patients with inoperable HCC underwent systemic CT. Patients received either combination cisplatin, interferon, doxorubicin and fluorouracil (PIAF) or single-agent doxorubicin. They were followed up during and for 8 weeks after CT. In 102 patients, 59 (58%) developed hepatitis amongst whom 37 (36%) were attributable to HBV reactivation. Twelve (30%) died of HBV reactivation. CT was interrupted in 32

patients (86%) with reactivation and 54 (83%) without reactivation (P > 0.05). The median survivals were 6.00 and 5.62 months, respectively (P = 0.694). Elevated baseline alanine aminotransferase (ALT) was found to be a risk factor.

The study concluded as HBV reactivation is a common cause of liver damage during CT in HBsAg-positive HCC patients. The only identifiable associated risk factor was elevated pre-treatment ALT.

A case was presented in the journal of breast cancer about the reactivation of hepatitis B virus in a breast cancer patient receiving CAF chemotherapy. A 68 year old patient a case of breast cancer received adjuvant chemotherapy CAF regimen without steroids. On day 27 , patient developed reactivation of hepatits b virus.

Patient was treated with symptomatic management and interferon with steroids and entecavir. But patient died of reactivation.

In another study done at Iran research centre of gastroenterology and liver disease at Tehran studied about the impact of immunosuppression and chemotherapy on reactivation of hepatitis B virus, concluded that Chemotherapy drugs, biological medications that are used to treat cancer, may cause hepatic side effects. Patients with pre-

existing viral hepatitis may be more susceptible to exacerbation of their underlying liver disease, and risk of drug-induced hepatotoxicity. They conducted a search on immunosuppression, and its impact on reactivation of viral hepatitis, using the electro-nic medical databases.Before starting chemotherapy, it is recommended to record the past history of liver disease and check for hepatitis B virus (HBV) and hepatitis C virus (HCV) serology. In immunosuppressed patients,radiation toxicity, graft versus host disease, hepatic veno-occlusive disease, acalculous cholecystitis, tumor infiltration, ischemia, other viruses such as CMV and herpes virus, and systemic infection should also be considered. Transplant recipients with serologic evidence of previous infection with hepatitis B or C, or those who receive organs from a seropositive donor, should have viral load levels monitored before and after transplantation and, may also require treatment. They believe that there is a role for prophylactic use of antiviral treatment in

patients at risk for HBV reactivation.

A systematic review of the trials which conducted on the reactivation of Hepatitis b and chemotherapy and role of Lamivudine prophylaxis concluded as-

This systematic review included prospective trials with lamivudine for prophylaxis against HBV reactivation in patients on chemotherapy. PubMed and MEDLINE databases were searched to identify suitable trials for inclusion in the analysis. Eligible trials were examined and variables (which included rates of hepatitis, HBV reactivation, HBV-related mortality, mutations that confer lamivudine resistance and adverse events) were assessed. Hepatitis was defined as a greater than threefold increase in baseline aminotransferase levels to above the upper limit of normal (58 IU/l) or an absolute increase of 100 IU/l compared with baseline. HBV reactivation was defined as a 10-fold increase in HBV DNA levels compared with baseline or an absolute increase of >1 10^9 copies/ml in HBV DNA levels.

The primary outcome measures were rates of hepatitis and HBV reactivation. Secondary outcome measures included adverse events, HBV-related mortality and mutations that conferred lamivudine resistance.

Results

In total, 10 trials with 173 patients were included in the analysis (one randomized, controlled trial; four prospective trials with historical controls; five prospective case series). Nine trials were performed in adult

populations and one trial in a pediatric population. The dose of lamivudine was 100 mg daily in the adult studies and 3 mg/kg body weight daily in the pediatric study. Lamivudine prophylaxis was administered 7–19 days before chemotherapy in seven studies, and on the first day of chemotherapy in three trials. Lamivudine therapy ended on the last day of chemotherapy in one trial, 1–3 months after chemotherapy in seven trials and 1 year in two trials. Duration of follow-up ranged from 2 months to 2 years after chemotherapy. The rate of hepatitis in patients who received lamivudine prophylaxis was 9.2% (range 0.0–20.0%) compared with 54.0% (range 33.0–67.0%) in patients who received placebo. The rate of HBV reactivation in patients who received lamivudine was 8.7% (0.0–24.0%) compared with 37.0% (range 29.0–56.0%) in patients who received placebo. Three deaths related to HBV reactivation occurred (two patients on lamivudine and one patient on placebo).Three studies monitored the emergence of mutations that conferred lamivudine resistance, and one trial identified two mutant strains among 46 patients (4.9%). There were no adverse events that led to dosage limitation or cessation of treatment.

Similarly in a study published in journal of liver in december 2004 done by Dai. MS, Wu PF, Shvu RY, Lu JJ, Chao Ty regarding Hepatitis B virus reactivation in breast cancer patients undergoing cytotoxic

chemotherapy and the role of preemptive lamivudine administration concluded that The test group consisted of 11 female patients with BC who were seropositive for hepatitis B surface antigen (HBsAg). Of these, 10 patients were treated in an adjuvant setting and one for metastatic disease. Lamivudine was given from the start of chemotherapy and was maintained until 1 month after the last infusion of chemotherapy. The control group consisted of nine historical BC patients carrying HBV and received similar systemic chemotherapy without preemptive lamivudine. Variables including HBsAg, HBV envelope antigen, anti-HBV envelope antibody, serial serum alanine transaminase (ALT), quantitative HBV viral DNA analysis, and HBV-DNA precore promoter and precore sequence were monitored. All patients tolerated lamivudine well without development of evident HBV reactivation or overt hepatitis. Serum ALT remained unchanged without rebound hepatitis after cessation of chemotherapy and withdrawal of lamivudine.

RATIONALE OF PROPOSED STUDY:

The incidence of reactivation of hepatitis b is well established in the management of hematological malignancies and high dose chemotherapy. The role of prophylactic lamivudine in the management of hematological malignancy with chemotherapy in the chronic inactive

hepatitis b infection with HBs Ag positive patients and also in patients with past history of Hepatitis b even without a chronic carrier state.(105)

This study is done to know the incidence of reactivation of hepatitis b virus in chronic carriers of HBsAg positive patients in the south Indian set up. This study will give a picture of reactivation of HBV in common malignancies such as carcinoma stomach , breast cancer and hepatocellular carcinoma treated with common chemotherapies such as cisplatin based or adriamycin based chemotherapy. Based on the study the role of prophylactic Lamivudine in the management of solid malignancies can be established which may be cost effective and decreases the morbidity and mortality associated with HBV reactivation.(96-102)

AIM OF THE STUDY

In this study

1. To determine the hepatitis B virus carrier state in patients receiving chemotherapy

2. To determine the incidence of reactivation of chronic carrier HBs Ag positive patients who underwent chemotherapy .

3. To assess the possibility of follow up of the carrier patients with serological and liver function tests for reactivation of Hepatitis B virus.

SUBJECTS AND METHODS

1.Inclusion criteria:

1.1Among the patients reported at medical oncology department,

1.1.1.Pathogically confirmed malignancy either by FNAC or biopsy histopathology report.

1.1.2. patients with hepatocellular carcinoma- confirmed by image guided FNAC or USG/ CT imaging suggestive of HCC with elevated S.AFP.

1.1.3.patients with malignancy planned for chemotherapy

- neoadjuvant chemotherapy

-adjuvant chemotherapy

- palliative chemotherapy- for metastatic and recurrent lesions.

1.2. Performance status ECOG- 2{zubrod score}

1.3. complete hemogram with in normal limits

WBC Tc- > 1,500cells/mm3

Platelets >1,00,000cells/mm3

Hemoglobin> 10gm%

(or corrected with packed cell transfusion)

1.4. Renal function

Blood urea : < 40 mg%

S. Creatinine: < 1.2mg%

1.5 Liver function test:

Total bilirubin <2 mg%

SGOT/SGPT: < 1.5 times the upper limit of normal

S.ALP : < 1.5 times the upper limit of normal

1.5.Cardiac function

ECHO: ejection fraction > 60%

ECG: within normal limits

1.6. Age > 18 yrs

1.7. Viral markers : HBs Ag positive

1.8. Signed specific consent form prior to study

2.EXCLUSION CRITERIA:

2.1. known case of HBs antigen positive without proof of malignancy

2.2. patients with proof of malignancy and HBs antigen positivity but not on chemotherapy as per the study protocol

2.3. known case of HBs antigen positive patients already on T.Lamivudine prophylaxis.

2.4. previous or present history of other immunesuppressive drugs

2.4.1. patients already on steroids for other comorbid medical conditions and as a treatment of malignancy except dexamethasone used as antiemetic prophylaxis and treatment.

2.4.2. patients already on T.cyclophosphamide, azathioprine, cyclosporine, etc

2.5. patients with history of autoimmune disorders are excluded

2.6. patients with history of uncontrolled diabetes mellitus, and history of congestive cardiac failure, chronic kidney disease.

2.7. patients with decompensated liver disease
Total bilirubin > 2 mg%

Elevated SGOT/SGPT > 1.5x UNL

Elevated ALP > 1.5x UNL

Low albumin < 4gm%

Albumin / globulin ratio reversal

(imaging suggested of cirrhosis with coexisting liver sol suggestive of hepatocellular carcinoma and elevated tumor markers with normal LFT are included in the study)

2.8. coexisting viral infections such as human immune deficiency virus are excluded.

2.9. patients with history of jaundice within 6 months previous to chemotherapy are excluded.

2.9. patients with coexisting HCV antibodies positive are excluded

2.10. previous history of chemotherapy and radiotherapy.

2.11. previous history of malignancy treated surgically other than included in the study (patients with history of malignancy previously treated with surgery only but not with chemotherapy or

radiotherapy now with metastatic or recurrent disease and planned for 1st line chemotherapy are included in the sudy)

2.12. performance status > 3

2.13. patients with evidence of malignancy planned for chemotherapy with HBs antigen positive patients but with anti HBc positive patients, HBe antigen positive and HBV DNA positive are excluded from the study.

2.15 patients with severe and active comorbid medical and surgical conditions.

2.16. pregnant and nursing mothers.

2.17 age < 18 yrs and > 65 yrs.

2.18. patients requiring dose modification due to renal or hepatic dysfunction are excluded from the study.

DATA COLLECTION:

Individual patients data collected included:

1. Proof of malignancy

2. Imaging with tumor markers (specific for the individual malignancy)

3. Clinical features and symptoms

4. Clinical examination of the patient prior to chemotherapy and every chemotherapy cycles.

5. Complete hemogram, blood sugar, s.electrolytes

6. Renal function test.

7. Liver function test.

8. Serological markers for HBV, HCV, HIV

9. (5),(6),(7),- are repeated prior to every chemotherapy cycles

10. Documentation of HBV reactivation by serological markers.

METHODOLOGY OF THE STUDY:

All the patients who attended medical oncology opd with proof of malignancy were evaluated and staged with necessary investigation. Patients were planned for chemotherapy as per the recommendations and included in the study protocol. Patients then counseled for testing the serological markers of HBV, HCV and HIV.

Patients were then routinely investigated with complete hemogram, renal function test and liver function test. Patients who were HIV positive and HCV positive were excluded from the study . Patients who were found to be positive for HBs antigen positive were evaluated for further serological markers of HBV to rule out active infection or chronic active infection.

Patients were advised to undergo serological markers –HBe antigen, ANTI HBc antibodies and HBV DNA . Patients found to be positive for any of the above markers were excluded from the study as they have chronic active infection or acute infection .

Patients who were not fit for chemotherapy as per complete hemogram, renal function test, liver function tests, are excluded from the study. Patients were counseled about the nature of study and requested to give informed written consent for the study.

Then patients were included in the study and were investigated with prechemo investigations necessary for the chemotherapy schedule. Patients were treated with chemotherapy as per the study protocols. Patients were advised to do complete hemogram ,renal function test and liver function test prior to every chemotherapy cycle. Patients with low WBC total count or absolute neutrophil count were treated with inj. G-

CSF till count normalized and then started on next cycle chemotherapy. Patients with low hemoglobin and low platelet count were treated with packed cell transfusions and concentrated platelet transfusions. Till then chemotherapy was delayed Patients with elevated renal parameters were evaluated for further renal function test to rule out pre renal or intra renal failure. If patient had prerenal failure treated symptomatically till the serum creatinine and blood urea normalized and then started on chemotherapy. Patients with intra renal failure were treated for the same and are excluded from the study as dose modification were not allowed as per study.

All the patients included in the study were evaluated for the liver function serially prior to every chemotherapy cycle. Patients who found to have elevated bilirubin or SGOT / SGPT or S.ALP. or GGT were investigated further to rule out reactivation. Patients were again reevaluated with serological markers HBe antigen, ANTI HBc antibodies and HBV DNA. Patients who were positive for any of the above markers were taken as reactivation of the hepatits B virus.

CHEMOTHERAPY SCHEDULES in THE STUDY:

1. BREAST CANCER:

Treated with FAC

Inj . 5- Fluro uracil 500mg/m2 i.v.

Inj. Adriamycin 50mg/m2 i.v.

Inj. Cyclophosphamide 500mg/m2 i.v.

Every 21 day cycle

2. **LUNG CANCER:**

Treated with P.E.

Inj . Cisplatin 80mg/m2 divided in three divided doses. D1-D3.i.v.

Inj. Etoposide 100mg/m2 D1-D3. i.v.

Every 28 day cycle

3. **CARCINOMA of STOMACH:**

Treated with cisplatin and 5-FU

Inj. Cisplatin 25 mg/m2 D1-D3,i.v.

Inj. 5-flurouracil 750mg/m2 D1-D3 , i.v.

Every 28 day cycle

4. CA. ANAL CANAL.

Treated with cisplatin and 5-FU

Inj. Cisplatin 100mg/m2 in divided doses given in D1-D3.i.v.

Inj. 5- flurouracil 1000mg/m2 D1-D3. i.v.

Every 28 day cycle.

5. CARCINOMA of OVARY:

Treated with cisplatin and cyclophosphamide

Inj. Cisplatin 100mg/m2 in divided doses in D1-D3. i.v.

Inj. Cyclophosphamide 600 mg/m2 D1. i.v.

Every 28 day cycle.

6. OSTEOSARCOMA:

Treated with cisplatin , adriamycin and cyclophosphaminde

Inj. Cisplatin 100mg/m2 in divided doses D1-D3 .i.v.

Inj. Adriamycin 25mg/m2 D1-D3.i.v.

Inj. Cyclophosphamide 400mg/m2 D1-D3.i.v.

Every 28 day cycle.

7. CARCINOMA of ESOPHAGUS:

Treated with cisplatin and 5-Fu

Inj. Cisplatin 60mg/m2 in divided doses D1-D3. i.v.

Inj. 5-Fluro Uracil 750mg/m2 D1-D3.i.v.

Every 21 day cycle.

8.RENAL CELL CARCINOMA:

Treated with gemcitabine and vinblastine

Inj. Gemcitabine 1000mg/m2 . D1,D8,D15. i.v.

Inj. Vinblastine 8mg/m2 D1.i.v.

Every 21 day cycle.

9. SECONDARIES LIVER with UNKNOWN PRIMARY:

Inj. Cisplatin 60mg/m2 in divided doses D1-D3. i.v.

Inj. 5- flurouracil 750 mg/m2 D1-D3. i.v.

10. CARCINOMA COLON:

Treated with FOLFOX-4

Inj oxaliplatin 85 mg/m2 i.v. D1. i.v.

Inj. 5- flurouracil 1000mg/m2 D1 & D2. i.v.

Inj. Leucovorin 200mg/m2 D1 & D2. i.v.

Schedule repeated every 14 days.

11. PERIAMPULLARY CARCINOMA:

Treated with cisplatin and gemcitabine

Inj. Cisplatin 60 mg/m2 in divided doses D1-D3. i.v.

Inj. Gemcitabine 1.2gm/m2 D1, D8, D15. i.v.

Every 21 day cycle.

12. HODGKINGS LYMPHOMA:

Inj. Adriamycin 25mg/m2 i.v. D1 & D15

Inj .Bleomycin 10U/m2 i.v. D1-D15

Inj. Vinblastine 6 mg/m2 .i.v. D1-D15

Inj. Dacarbazine 375mg/m2. i.v. D1-D15

Every 28 day cycle.

13. HEPATOCELLULAR CARCINOMA:

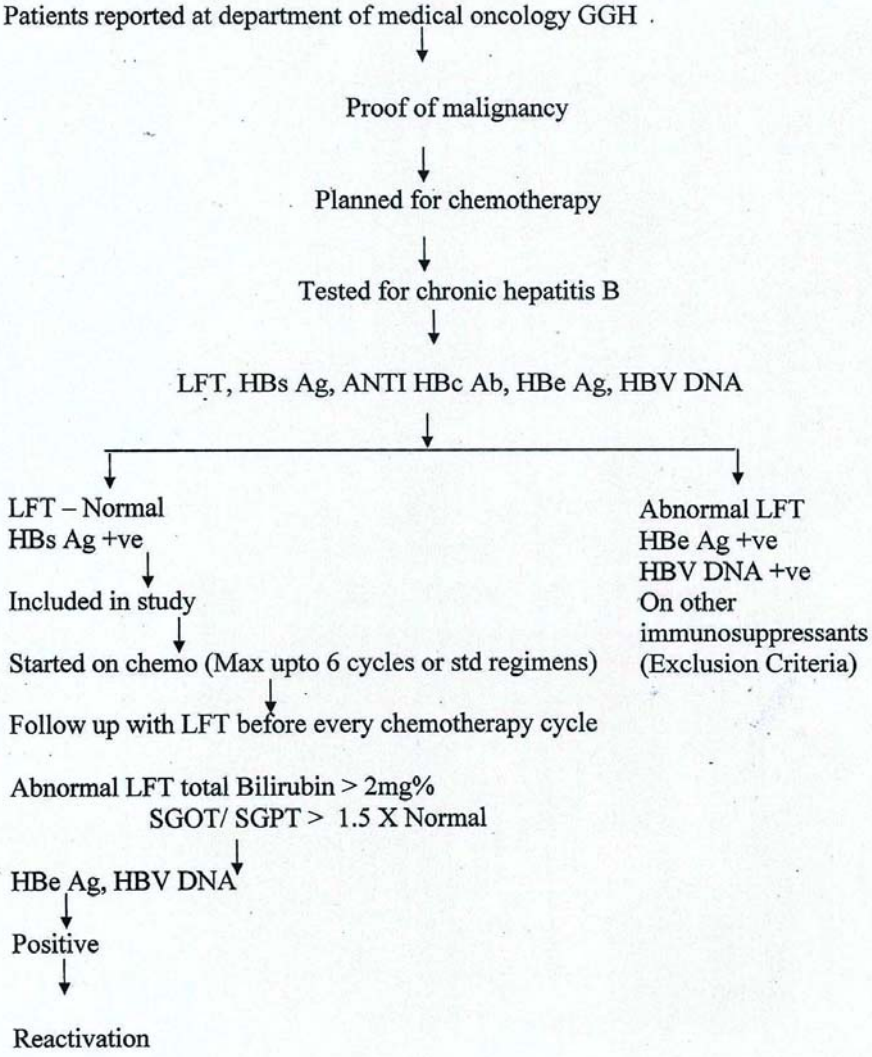
Inj. Cisplatin 60mg/m2 in divided doses D1-D3. i.v

Inj. Adriamycin 60 mg/m2 D1. .i.v.

Inj. 5- fluro uracil 750 mg/m2 D1-D3. i.v.

Every 21 day cycle.

METHODOLOGY:



RESULTS AND ANALYSIS

Between June 2009 and December 2010 all the patients registered at medical oncology opd GGH were evaluated for the serological status. All the patients underwent serology tests ELISA for HIV, ELISA for HBs AG and ELISA for Anti HCV antibodies. Totally 1850 patients were examined among them 62 patients were found to be HBS antigen positive. The HBS antigen positive patients are about 3.35% of the total patients underwent serological tests.

There were about 20 female patients and 42 male patients were diagnosed as hepatitis b antigen positive .Among the 62 patients one patient had coexisting HIV infection and not included in the study, one patient had coexisting HCV antibodies positive and hence not included in the study. Among the 60 patients only 43 patients had met the eligibility criteria for the study and included in the study. Those 17 patients who do not met the criteria for the study 11 patients presented with jaundice and 3 patients had chronic renal disease and 2 patients had congestive cardiac failure and not included in the study. One patient had rheumatoid arthritis and already on steroids and excluded. Among the 11 patients with jaundice 8 patients were diagnosed as hepatocellular

carcinoma and 2 were carcinoma stomach with liver secondaries and one with carcinoma pancreas with liver secondaries.

Table 1:

1.	No of patients screened	1850
2.	No of patients HBs Antigen +ve	62
3.	No of patients eligible for study	43
4.	Patients excluded from the study	19
	1.Patient with associated HIV	1
	2. Patient with associated HCV	1
	3.Patietns presented with jaundice Hepatocellular carcinoma Carcinoma stomach with liver sec Carcinoma pancreas with liver sec	11 8 2 1
	4. Patients with CKD	3
	5.Patients with CCF	2
	6. Patient with rheumatoid arthritis already on steroids	1

Within the 43 patients 3 patients developed elevated blood urea and serum creatinine and nephrologist advised to stop cisplatin and hence excluded from the study. None underwent dialysis and managed conservatively. Two patients developed severe grade 4 mucositis and febrile neutropenia while on adriamycin based chemo and one patient died of septic complications. Atlast 38 patients in the study were

examined and monitored for the reactivation of HBV during chemotherapy taken for the study.

Table 2:

S.No.	Maliganancy	No of patients in the study
1.	Carcinoma stomach	9
2.	Carcinoma lung	8
3.	Carcinoma breast	7
4.	Hepatocellular carcinoma	5
5.	Hodgkins lymphoma	2
6.	osteosarcoma	2
7.	Carcinoma colon	2
8.	Carcinoma ovary	2
9.	Sec neck and sec liver unknown primary	Each 1 (2)
10.	Renal cell ca, Ca anal canal, RCC, Periamp ca	Each 1 (4)
	total	43
	Patients excluded from the study because of discontinuation of chemo due to other reasons other than reactivation of HBV	5
	Raised renal parameters	3(one in each HCC,ca lung and stomach)
	Febrile neutropenia with sepsis	2(one in breast and stomach)

The age of the patients range from 18 to 64 yrs included in the study .median age was 52 yrs. Among 38 patients 11 patients were female and 27 male patients were in the study. There were 9 diabetic patients adequately controlled blood sugar with insulin and serially monitored during every chemotherapy cycles. All the patients were advised to changed to insulin even though adequately controlled with OHAs. With the guidance of diabetologist all were put on insulin injections. All the diabetic patients were excluded of diabetic nephropathy and were monitored with urine microalbuniuria and blood urea and creatinine during every cycle while on cisplatin based chemotherapy.

Among the 38 patients 5 patients were known case of ischemic heart disease with normal LV function. All those patients were on antianginal drugs . About 8 patients were hypertensive and 6 patients were on T. amlodipine and 2 patients were on T. enalapril and atenolol. About 5 patients gave past history of anti tuberculous treatment. Both the Hodgkin lymphoma patients received ATT at a local hospital prior to referral here. Two lung cancer patients also gave history of ATT , one patient 10 yrs ago and another about 22 yrs ago. One carcinoma stomach patient gave history of ATT 5 yrs ago.

About 16 patients gave past history of jaundice and 2 patients gave history twice episode of jaundice one within the past 2 yrs then. Both the patients with 2 episode of jaundice were diagnosed as hepatocellular carcinoma. Among the fourteen patients eight were diagnosed as carcinoma stomach , three were carcinoma lung one breast cancer , one colon cancer and one carcinoma anal canal. All the 18 patients underwent native treatment during the jaundice.

Table 3: comorbidities

1.	No of patients with diabetes mellitus controlled	9
2.	Patients with hypertensive	8
3.	No of patients with IHD	5
4.	Previous history of jaundice	16
	2 episodes of past history of jaundice	2
	Hepatocelllar ca with prev h/o jaundice	2
	Carcinoma stomach	6
	Carcinoma lung	4
	Carcinoma breast	1
	Carcinoma colon	1
	ostoesarcoma	1
	Carcinoma anal canal	1

Among the 38 patients who underwent chemotherapy as per the study protocol, 8 patients developed reactivation. All the patients who developed reactivation presented with jaundice with elevated serum transaminases. They were again tested for serological markers for Hepatitis B. All the patients were positive for HBe antigen and HBV DNA positive who were previously negative.

Table 4:

No	Malignancy	No of patients reactivated
1.	Hepatocellular carcinoma	2
2.	Carcinoma of breast	1
3.	Carcinoma stomach	2
4.	Periampullary carcinoma	1
5.	osteosarcoma	1
6.	Carcinoma lung	1

Table. 5

LFT profile of the patients who had reactivation of HBV and serological markers

No	Patients	Bilirubin total-DB/IDB mg%	SGOT IU/L	SGPT IU/L	ALP IU/L	S. Albumin gm%	ANTI HBc Ab	HBe Ag	HBV DNA
1.	HCC	6.7-4.3/2.4	420	650	300	4.2gm %	positive	positive	positive
2.	HCC	5.4-3.4/2	880	1040	550	3.0gm %	positive	positive	positive
3.	Ca stomach	5.8-3.2/2.6	440	400	350	4gm%	Positive	positive	NA
4.	Ca stomach	8.2-5.4/2.8	800	1250	550	3gm%	positive	positive	positive
5.	Ca lung	4.5-2.5/2	400	350	500	4.5	Positive	positive	NA
6.	Ca breast	5.5-3.5/2	350	400	300	4	Positive	positive	Positive
7.	Peri amp ca	10-6.4/3.6	540	550	600	3.5	positive	positive	positive
8.	osteosarcoma	3.5-2/1.5	300	550	800	2.8	Positive	positive	positive

Among the 38 patients , 8 patients underwent reactivation of HBV. Malignancy taking in the study 2 patients with hepatocellular carcinoma, 2 patients with carcinoma stomach underwent reactivation. One patient in each of ca breast, osteosarcoma, ca lung and periampullary carcinoma

forms the remaining. Among the four patients of hepatocellular carcinoma 2 patients underwent reactivation, 2 patients among the 7 ca stomach patients underwent reactivation, 1 patient among the 6 ca breast patients,1 among the 2 osteosarcoma patients and one patient among the 7 ca lung patients underwent reactivation Only one patient with periampullary carcinoma included in the study had reactivation of HBV.

Table: 6

S. No.	Malignancy	Patients in study	Reactivation	%
1.	Hepatocellular carcinoma	4	2	50%
2.	Carcinoma stomach	7	2	28.56%
3.	Carcinoma breast	6	1	16.66%
4.	osteosarcoma	2	1	50%
5.	Carcinoma lung	7	1	14.28%
6.	Periampullary carcinoma	1	1	100%
	Total	38	8	21.05%

Among the 8 patients 7 patients received palliative chemotherapy for metastatic disease or advanced stage or relapse patients . Only one carcinoma stomach patient received adjuvant chemotherapy underwent reactivation of HBV.

DISCUSSION

The reactivation of Hepatitis B virus in the patients receiving chemotherapy has been proven in many studies ,but most of the studies are involving the treatment of hematological malignancies and the use of Rituximab. In various studies the incidence of reactivation of Hepatitis b in lymphoma(81-83) patients receiving chemotherapy is about 40%.the incidence of reactivation n patients receiving rituximab is about 60%. A study in Hong Kong in breast cancer patients receiving chemotherapy with alkylating agents along with steroids has high incidence of about 73%.

While comparing our study with the a study at Turkey(74) which had been done involving all solid tumors,in that study totally 59 patients of which 50 patients were of solid malignancy and 9 hematological malignancy patients,the incidence of reactivation was about 15%.

In our study totally 38 patients were included in the study and the incidence of reactivation is about 21% and totally 8 patients got reactivated which is significant because of the morbidity and mortality associated with reactivation of HBV and the delay in chemotherapy which may lead to progression of malignancy. Most of the patients got reactivation was treated for the metastatic disease with palliative

chemotherapy. Most of the patients got reactivated were treated with more immunosuppressive chemotherapy such as adriamycin and etoposide. Similarly many studies have shown that adriamycin based chemotherapy and steroids have shown increased incidence of reactivation of HBV. Most of the reactivation occurs between the second and fourth cycle of chemotherapy. There are few studies which showed late reactivation of hepatitis B virus even after completion of chemotherapy, but in our study none of the patients got reactivated after 3 months of follow up, but a longer term of follow up must be needed. In our study none of the patients had non hodgkins lymphoma in which most of the studies showed increased incidence of reactivation .

In our study all the 9 patients showed increased in the liver enzyme level as the earliest sign along with development of jaundice. So all the patients with Hepatitis S antigen positive on immunosuppressive therapy should undergo regular monitoring of liver function tests for early detection of reactivation of HBV and can be treated earlier to prevent mortality.

As in the literature review among the solid malignancies hepatocellular carcinoma has highest incidence of reactivation of HBV about 70%, followed by breast cancer about 40-60% in various studies. In

our study too out of 4 patients with hepatocellular carcinoma in the study 2 patients underwent reactivation.

Similarly patients with metastatic disease undergoing chemotherapy with HBsAg positive has increased incidence of reactivation probably because of advanced nature of disease and increased cancer burden which may lead to immune suppression .Out of 8 patients who had reactivation 7 patients underwent chemotherapy for metastatic or relapse disease. Age of the patient was not found to be significant in reactivation in our study.

As per our study the incidence of reactivation is about 21% even in the solid malignancies undergoing chemotherapy in patients with chronic HBs Ag carriers, which is significant and all the patients should be started on lamivudine prophylaxis to prevent reactivation. There is another subset of patients who are HBc antibodies positive but HBs Ag negative(90) , patients had infection but not chronic carriers, can undergo reactivation during chemotherapy which has not been accounted in our study, needs further studies in solid malignancies whether to start lamivudine prophylaxis for that patients too will be useful. (91-93,95)

CONCLUSION

FROM THE STUDY, we concluded that

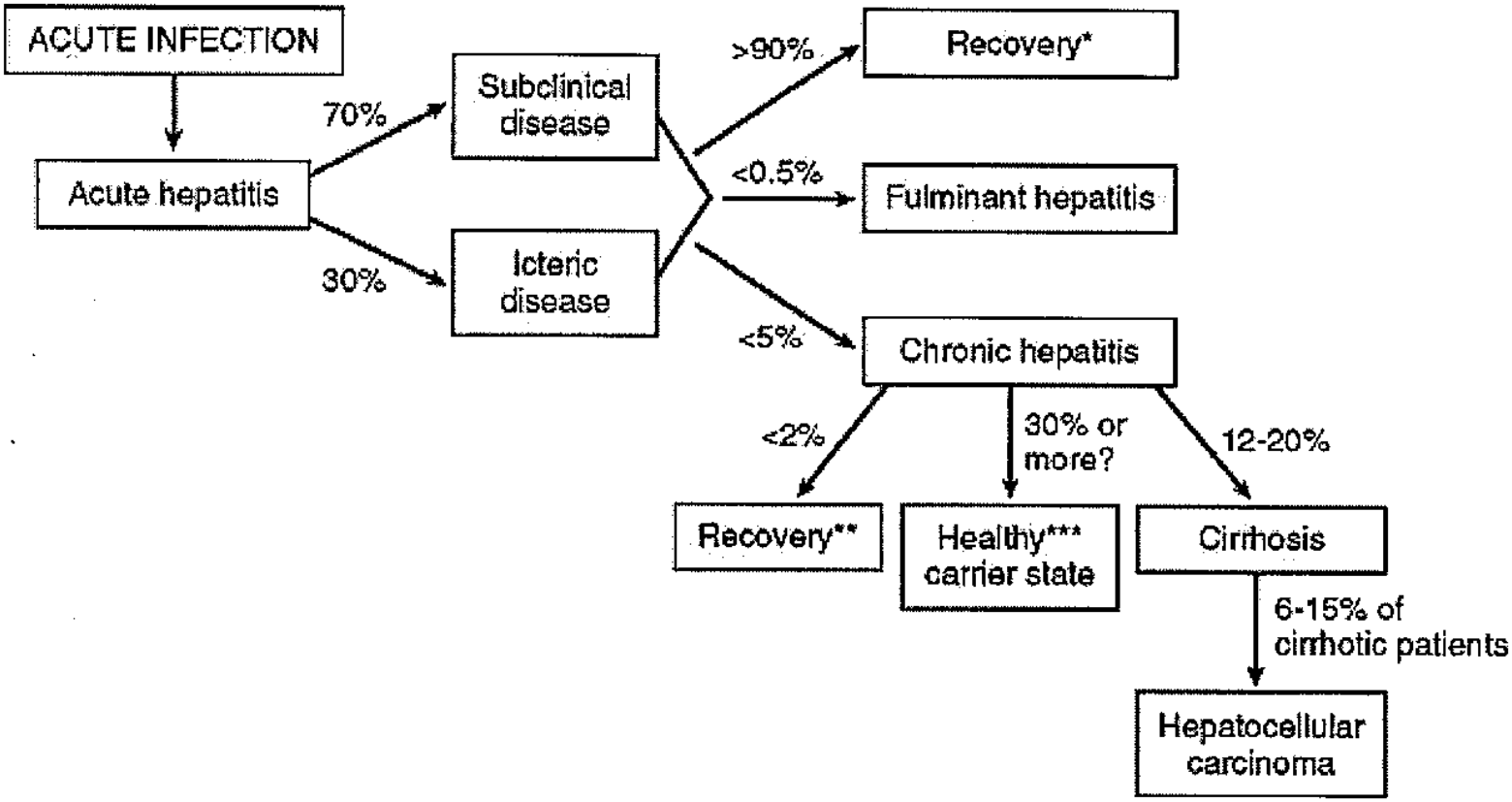
1. The overall incidence of chronic HBs antigen carrier state is about 3.35%

2. The incidence of reactivation of Hepatitis B virus in chronic HBs antigen patients receiving chemotherapy is 21% as we concluded from the study.

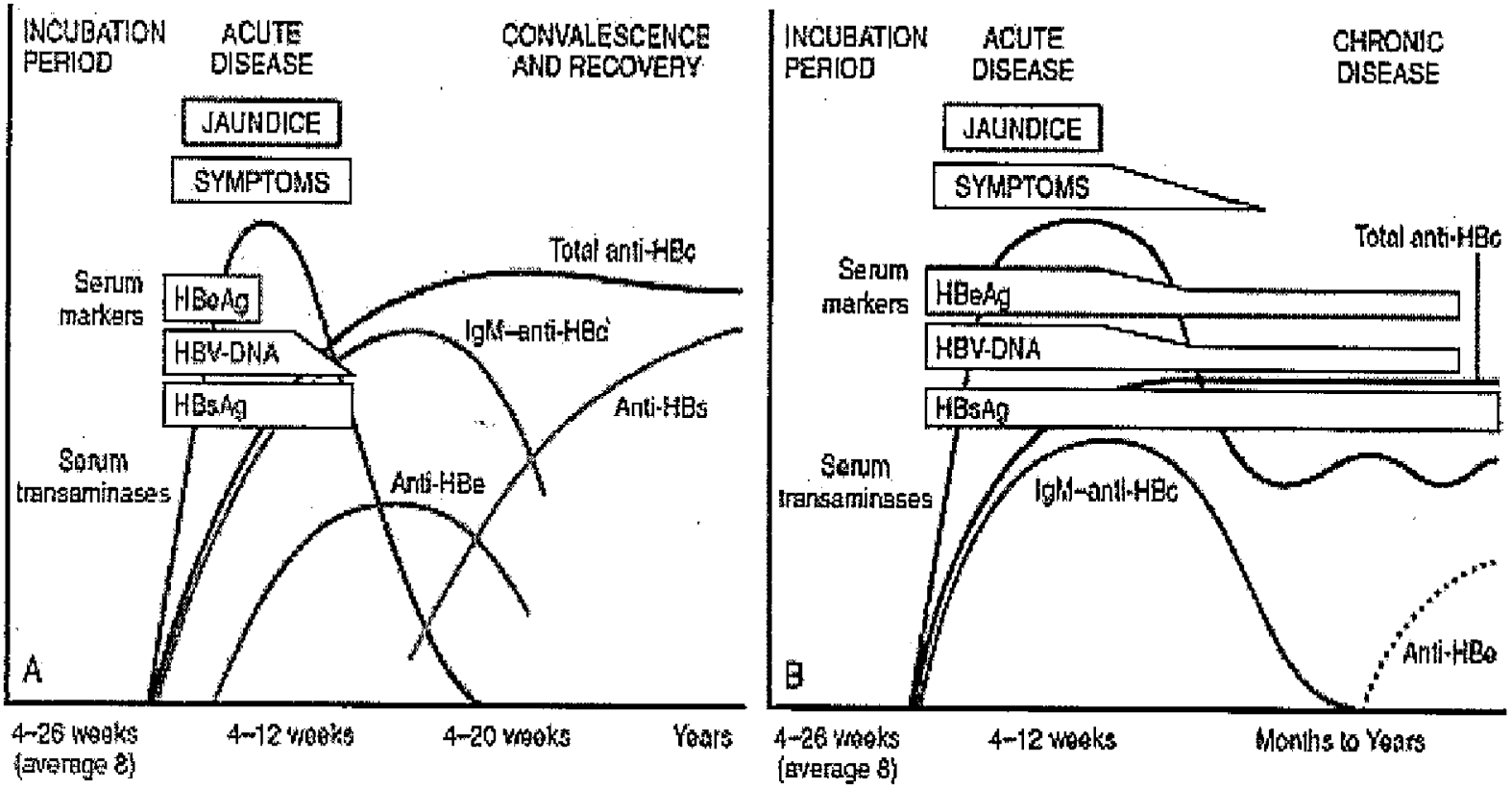
3. Patients who are on adriamycin based chemotherapy for the solid malignancies also had increased incidence of reactivation of hepatits B virus in HBs antigen chronic carriers.

4. Since patients with solid malignancy in chronic carrier HBs antigen state had high incidence of reactivation, we suggest that those patients should be treated with prophylactic Lamivudine .

Clinical Course of HBV



Serology of HBV



PROFORMA

NAME: M.O.-No:

AGE: SEX:

ADDRESS: OCCUPATION

DETAILS OF MALIGNANCY:

Malignancy –organ involved:

Type:

Stage:

Principle of treatment: palliative/ curative/adjuvant/neoadjuvant/induction

Chemo regimens/schedules:

Chemotherapy cycle:

CLINICAL FEATURES:

Symptoms:

H/O present illness:

Past history: DM/HT/ IHD/ PT/ BA/ COPD/ CKD/ DCLD/HIV

H/O STEROIDS/ANY IMMUNOSUPPRESANTS

H/O AUTO IMMUNE DISORDERS

Prev H/O radiotherapy and any other malignancy/chemotherapy

Personal history:

Diet

Smoking /Alcoholic

Sexual history –PMC/ EMC SAFE/UNSAFE

Family history:

H/O malignancy in family

H/O HBV in family

H/o congenital immunodeficiency disorders

Vitals:

1. Pulse
2. Temperature
3. Weight\height
4. BSA

General Examination:

Performance status:

Conscious

Orientation

Febrile

Pallor/ Cyanosis/Clubbing

Jaundiced

Pedal edema. / Gen lymphadenopathy

Cardiovascular system:

Respiratory system:

Per abdomen ex:

Central nervous system:

Local examination:

INVESTIGATIONS:

CBC: TC:

DC:

ESR:

HB%

PLATELETS

RFT: BUN:

CREATININE:

LIVER FUNCTION TEST:

TOTAL BILIRUBIN

DIRECT/ INDIRECT

SGOT/ SGPT

S. ALKALINE PHOSPHOTASE

S. PROTEINS

ALBUMIN/GLOBULIN

CHEST X-RAY:

USG ABDOMEN:

DIAGNOSTIC AND STAGING WORKUP FOR MALIGNANCY:

SEROLOGICAL MARKERS:

AT INITIATION OF CHEMOTHERAPY:

HBs Ag

ANTI HBc Ab

HBe Ag

HBV DNA

SEROLOGY FOR HIV

SEROLOGY FOR HCV

CHEMO CYCLE-1

CHEMO REGIMEN:

REGIMEN/ PERIOD:

CBC/RFT/LFT

CHEMO CYCLE-2

CHEMO CYCLE-3

CHEMO CYCLE-4

CHEMOCYCLE-5

CHEMOCYCLE-6

OTHERS

ONE MONTH AFTER CHEMOTHERAPY:

LFT

HBs Ag

HBe Ag

HBV DNA

ANTI HBc Ab

TWO MONTHS AFTER CHEMOTHERAPY:

LFT

HBs Ag

HBe Ag

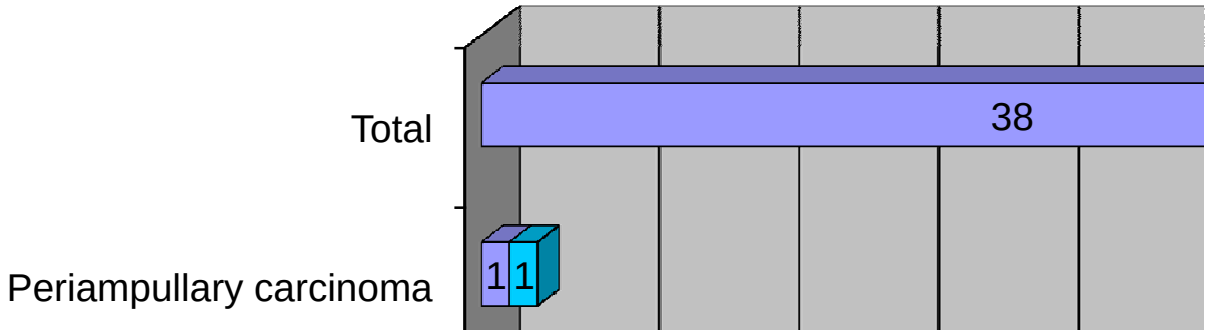
HBV DNA

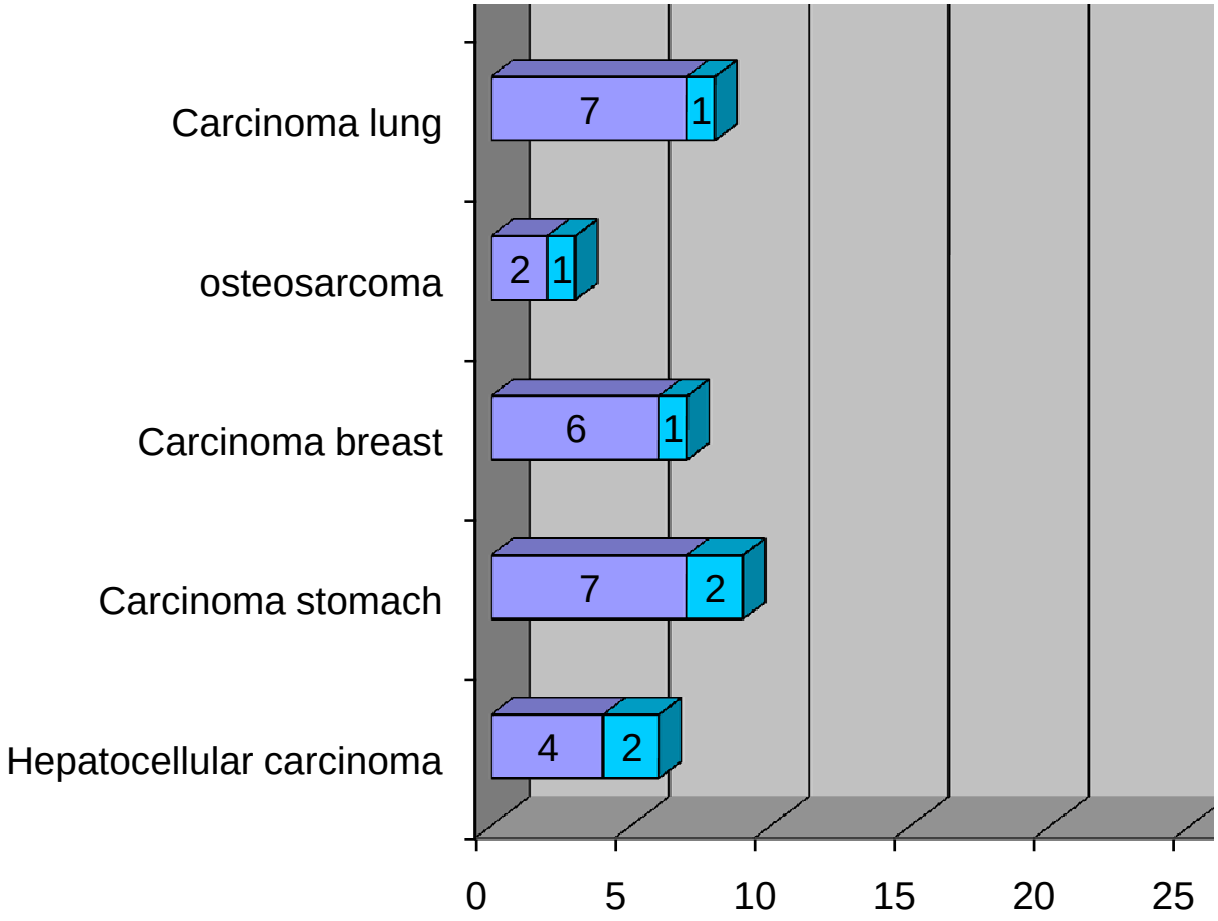
ANTI HBc Ab

Carcinoma stomach	9
Carcinoma lung	8
Carcinoma breast	7
Hepatocellular carcinoma	5
Hodgkins lymphoma	2
osteosarcoma	2
Carcinoma colon	2
Carcinoma ovary	2
Sec neck and sec liver unknown primary	2
Renal cell ca, Ca anal canal, RCC, Periamp ca	4

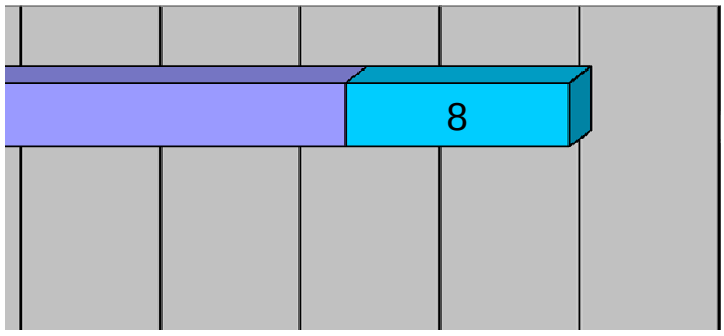
Hepatocellular carcinoma	2
Carcinoma of breast	1
Carcinoma stomach	2
Periampullary carcinoma	1
osteosarcoma	1
Carcinoma lung	1

43
62





Hepatocellular carcinoma	4	2
Carcinoma stomach	7	2
Carcinoma breast	6	1
osteosarcoma	2	1
Carcinoma lung	7	1
Periampullary carcinoma	1	1
Total	38	8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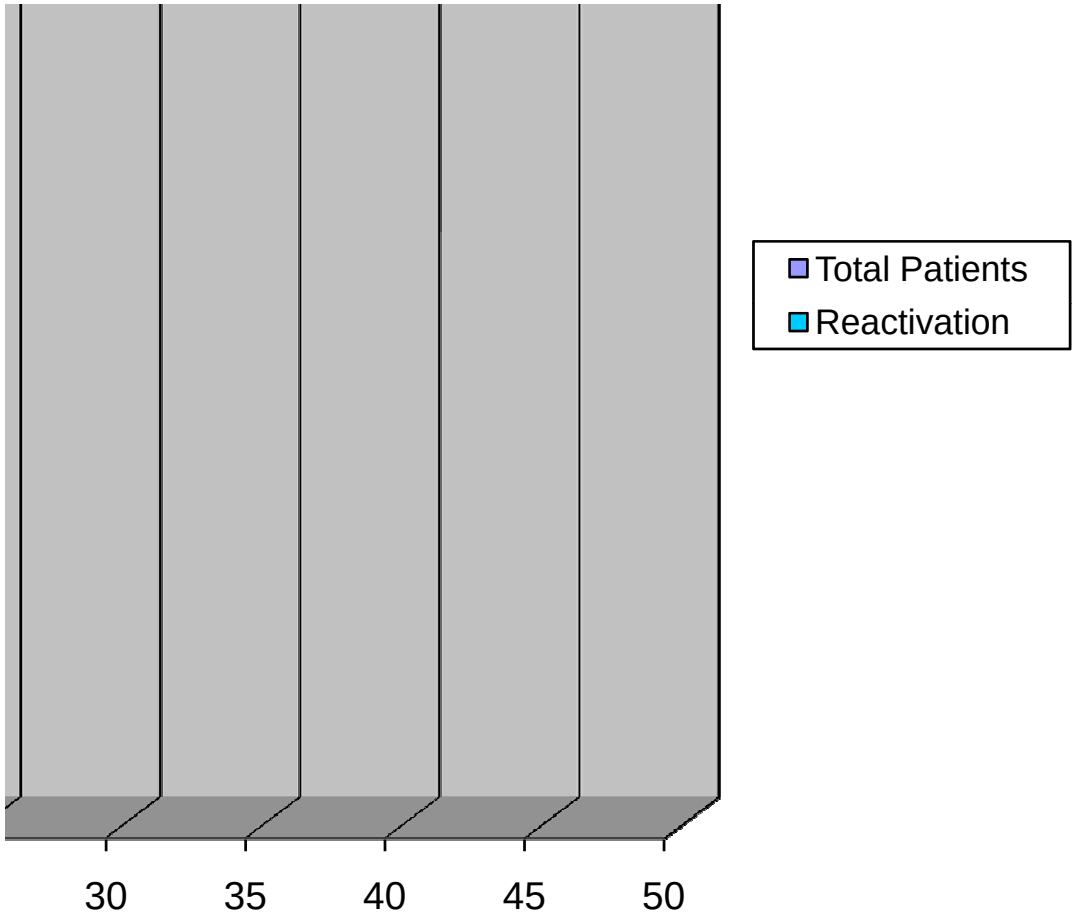
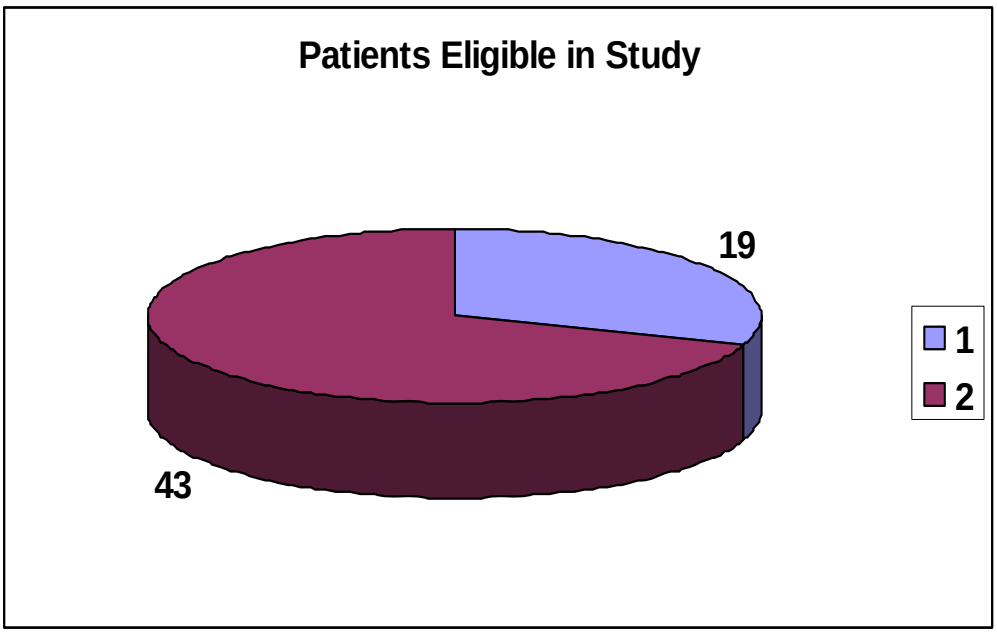
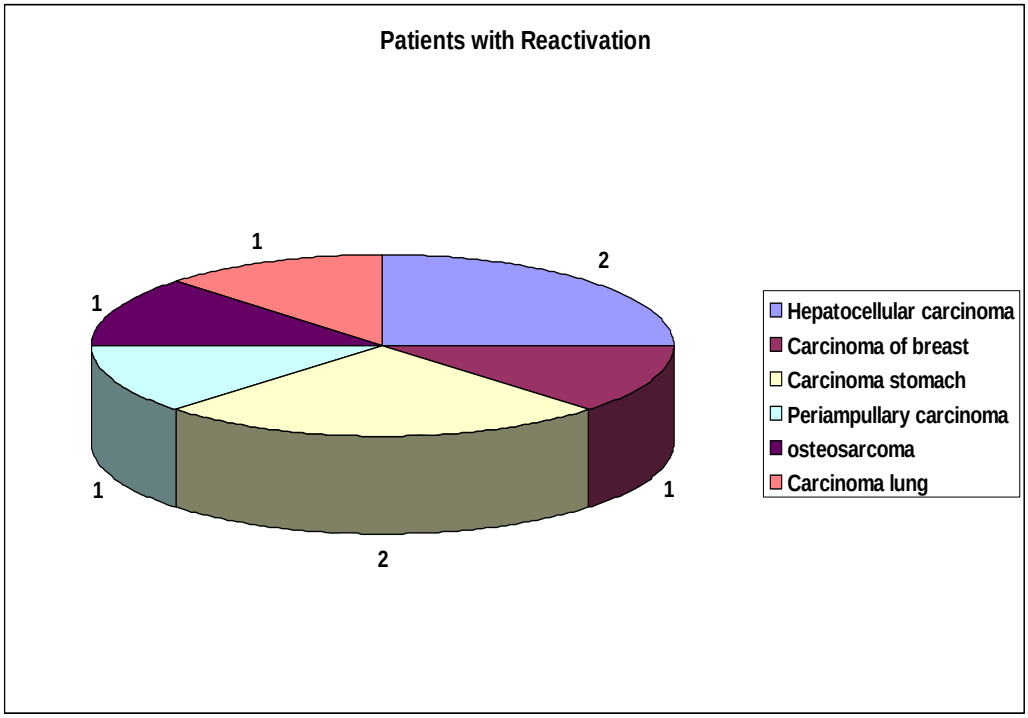
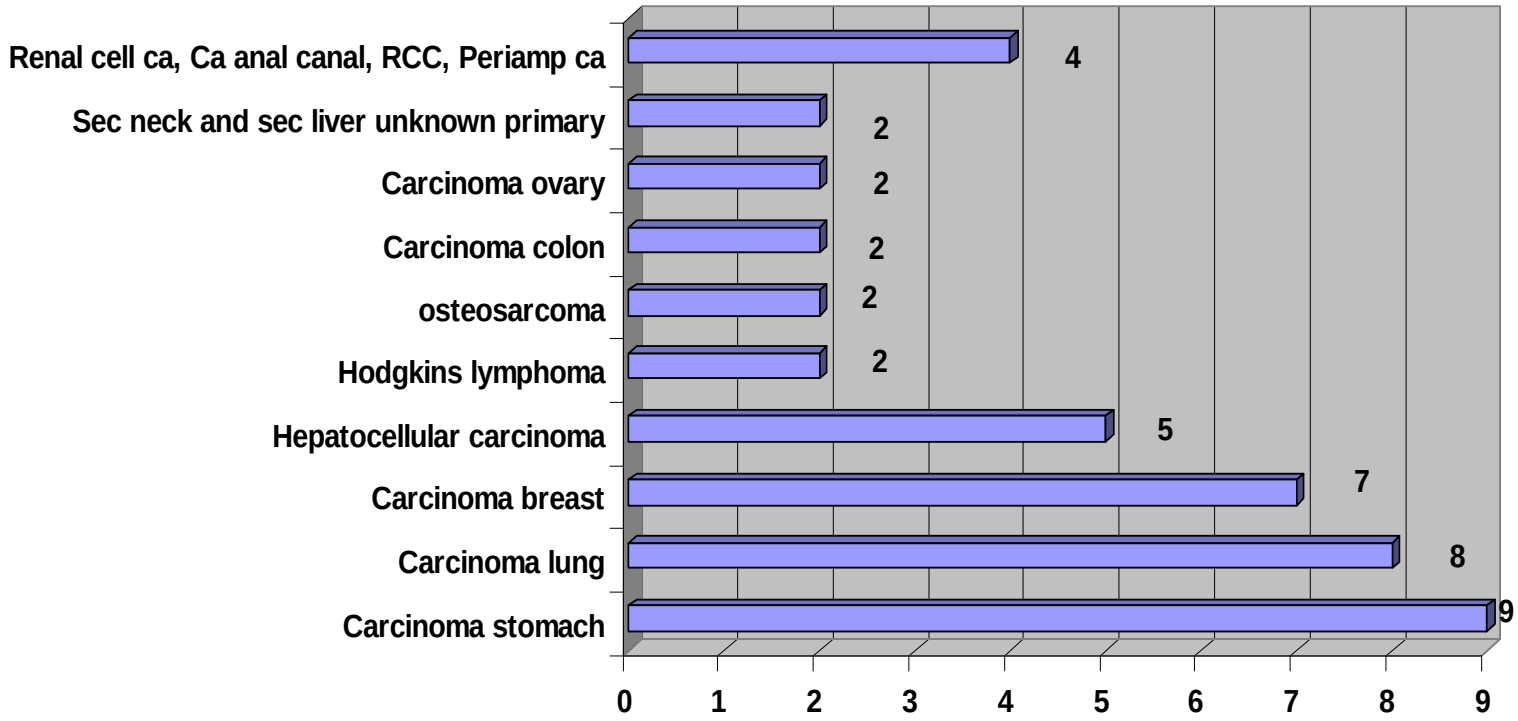
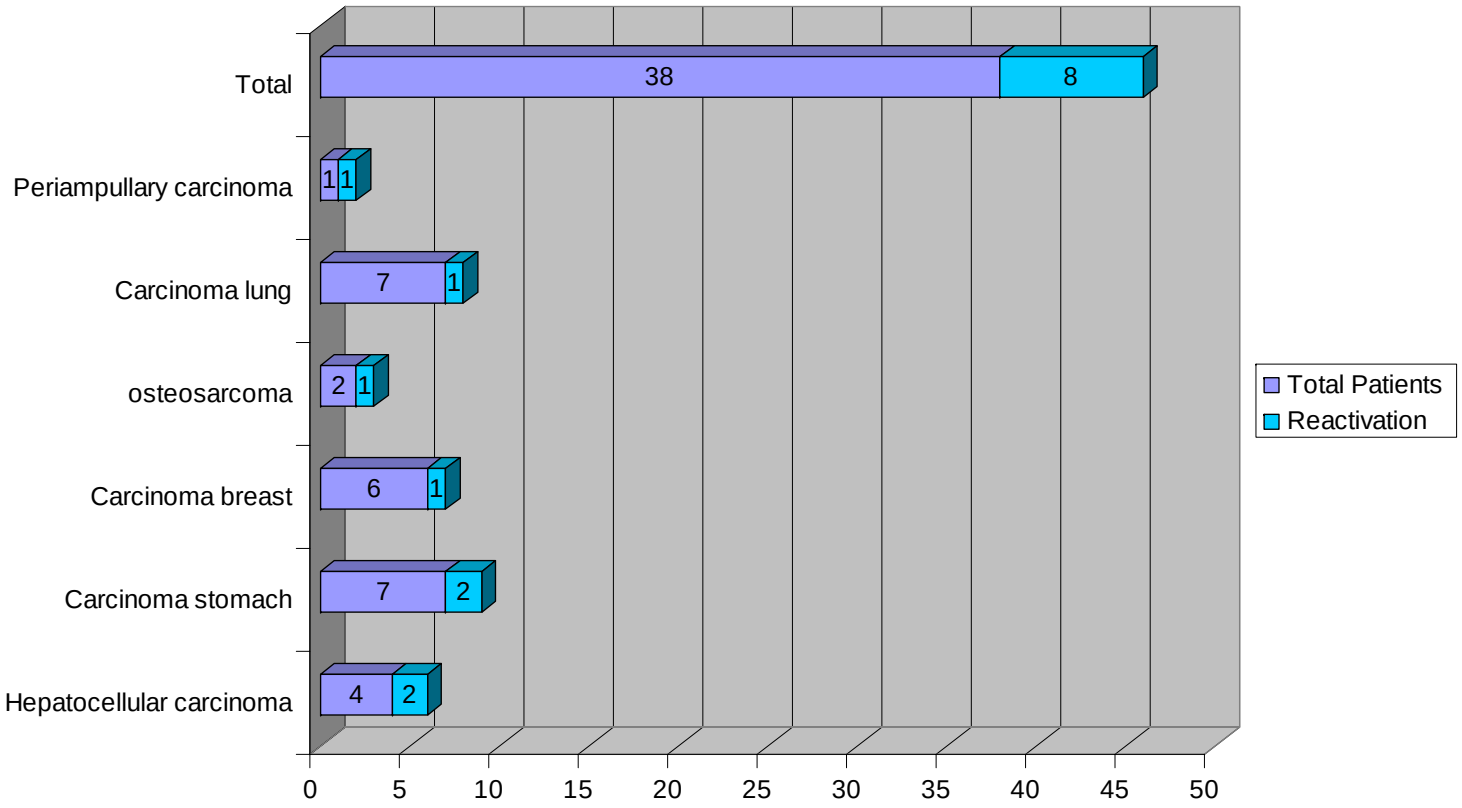

Total Patients
Reactivation
30
35
40
45
50


Patients Eligible in Study
19
43
1
2


Patients with Reactivation
1
2
1
1
2
1
Hepatocellular carcinoma
Carcinoma of breast
Carcinoma stomach
Periampullary carcinoma
osteosarcoma
Carcinoma lung

Patients with HBs antigen




Total
Periampullary carcinoma
Carcinoma lung
osteosarcoma
Carcinoma breast
Carcinoma stomach
Hepatocellular carcinoma
38
8
1
1
7
1
2
1
6
1
7
2
4
2
0
5
10
15
20
25
30
35
40
45
50
Total Patients
Reactivation

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