Reactivation of Hepatitis B Virus in Cancer Patients Receiving Chemotherapy

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ABSTRACT

Introduction: Hepatitis B virus reactivation (HBVr) is an important complication of immunosuppressive drug therapy. It can occur with active or resolved hepatitis B virus (HBV) infection with a clinical spectrum that ranges from mild elevations in liver tests to fulminant hepatic failure. HBV reactivation is defined as an abrupt increase in serum HBV DNA and alanine transaminase (ALT) levels in a patient with resolved or inactive HBV infection. Study aimed to determine the hepatitis B virus carrier state in patients receiving chemotherapy and determine the incidence of reactivation of chronic carrier HBsAg positive patients who underwent chemotherapy.

Material and methods: 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. 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.

Results: 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.

Conclusion: To conclude that the overall incidence of chronic HBs antigen carrier state is about 3.35%. The incidence of reactivation of Hepatitis B virus in chronic HBs antigen patients receiving chemotherapy is 21% as we concluded from the study. Keywords

Keywords: HBVr, Chemotherapy, Cancer, Liver

INTRODUCTION

Nearly one-third of the world's population has been infected with hepatitis B and the virus is endemic in many Asian countries. The average estimated carrier rate of hepatitis B virus (HBV) in India is 4%, with a total pool of approximately 36 million carriers.[1] 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 pyretherapy 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.[4] Anthracyclines and steroids are among the chemotherapeutic agents most often 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.[5] 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 analog, lamivudine. The commencement of antiviral prophylaxis prior to chemotherapy and its continuation until the 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. Study aimed to determine the hepatitis B virus carrier

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state in patients receiving chemotherapy and determine the incidence of reactivation of chronic carrier HBsAg positive patients who underwent chemotherapy.

MATERIAL AND METHODS

All the patients who attended the medical oncology department with proof of malignancy were evaluated and staged with the necessary investigation. Patients were planned for chemotherapy as per the recommendations and included in the study inclusion criteria. 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 underwent 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 the 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 intrarenal failure. If the patient had prerenal failure treated symptomatically until the serum creatinine and blood urea normalized and then started on chemotherapy. Patients with intrarenal failure were treated for the same and are excluded from the study as dose modification was not allowed as per the 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 hepatitis B virus.

RESULTS

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 to coexist 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 meet 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. 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. In the final 38 patients in the study were examined and monitored for the reactivation of HBV during chemotherapy taken for the study.

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.

Among the 38 patients 5 patients were known the case of ischemic heart disease with normal LV function. All those patients were on antianginal drugs.

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 18 patients underwent native treatment during jaundice.

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.

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 carcinoma 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.

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 patients receiving chemotherapy is about 40%.[6-8] The incidence of reactivation in patients receiving rituximab is about 60%.[9] While comparing our study with the study at Turkey[10] 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 an increased incidence of reactivation of HBV.[11] 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 nonhodgkins lymphoma in which most of the studies showed an increased incidence of reactivation.

In our study all the 9 patients showed increased in the liver enzyme level as the earliest sign along with the 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 the highest incidence of reactivation of HBV about 70%, followed by breast cancer about 40-60% in various studies.[12] 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 the advanced nature of the 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 relapsed 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[13], patients had an 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.[14-16]

CONCLUSION

The overall incidence of chronic HBs antigen carrier state is about 3.35%. The incidence of reactivation of Hepatitis B virus in chronic HBs antigen patients receiving chemotherapy is 21% as we concluded from the study. Patients who are on Adriamycin-based chemotherapy for the solid malignancies also had increased incidence of reactivation of hepatitis B virus in HBs antigen chronic carriers. 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.

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