RESEARCH ARTICLE

Hepatitis B and C Seroprevalence in Solid Tumors - Necessity for Screening During Chemotherapy

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Abstract

Background: Hepatitis B and C are the leading causes of liver diseases worldwide. For hematological and solid malignancy patients undergoing chemotherapy, increases in HBV DNA and HCV RNA levels can be detected which may result in reactivation and hepatitis-related morbidity and mortality. The aim of this study was to determine the seroprevalence of Hbs ag and Anti HCV positivity in patients with solid malignancies undergoing chemotherapy and consequences during follow-up. Materials and Methods: The files of 914 patients with solid malignancies whose hepatitis markers were determined serologically at diagnosis were reviewed retrospectively. All underwent adjuvant/palliative chemotherapy. For the cases with HBV and/or HCV positivity, HBV DNA and HCV RNA levels, liver function tests at diagnosis and during follow-up and the treatment modalities that were chosen were determined. Results: Of 914 cases, Hbs Ag, anti Hbs and anti HCV positivity were detected in 40 (4.4%), 336 (36.8%) and 26 (2.8%) of the cases respectively. All of the Hbs ag positive patients received prophylactic lamuvidine before the start of chemotherapy. In the Hbs ag and anti HCV positive cases, liver failure was not detected during chemotherapy and a delay in chemotherapy courses because of hepatitis was not encountered. Conclusions: Just as with hematological malignancies, screening for HBV and HCV should also be considered for patients with solid tumors undergoing chemotherapy. Prophylactic antiviral therapy for HBV reduces both the reactivation rates and HBV related mortality and morbidity. The clinical impact of HCV infection on patients undergoing chemotherapy is still not well characterized.

Keywords: Hepatitis B - hepatitis C - malignancy - lamuvidine

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Introduction

Hepatitis B virus (HBV) is a human carcinogen and chronic infection still remains as a major global health problem. Approximately a third of the world's population (2 billion people) has been infected with this virus and more than 350 million of them are chronically infected cases. Long term sequelae as cirrhosis, liver failure and hepatocellular carcinoma lead to 600,000-1000000 deaths annually (Custer et al., 2004; Lavanchy, 2004). Hepatitis C virus (HCV) is also one of the main causes of chronic liver diseases. The long term impact of HCV is highly variable as in HBV infection. The number of chronically infected cases is estimated to be more than 200 million worldwide (EASL, 2011). In Turkey, the seropositivity of Hbs ag has been reported as 3.4% in the western region; while as 8% in eastern and southeastern regions (Mehmet et al., 2005). Gurol et al documented the trends over 16 years in HBV and HCV seroprevalence among 2.4 million Turkish blood donors. They have reported that the overall prevalence was 4.19% for Hbs ag and 0.38% for HCV in Turkey (Gurol et al., 2006). In another study among healthcare workers, the prevalence of HCV was reported as between 1.2-4% (Yazici et al., 2010).

Since chemotherapy is highly immunosuppressive, it may cause increments in both HBV DNA and HCV RNA levels. For HBs Ag carriers the flares can occur despite normal serum alanine transferase (ALT) levels and low levels of circulating viral load and this leads to HBV related mortality and morbidity (Lau et al., 2003; Kohrt et al., 2006). For Hbs Ag seropositive cancer patients undergoing chemotherapy, HBV reactivation has been a well known complication, which may range from anicteric hepatitis to severe and sometimes fatal hepatic failure (Alagozlu et al., 2013). In 1990s, the reports about HBV reactivation mostly involved patients with hematologic malignancies (Soh et al., 1992; Nakamura et al., 1996; Kumagai et al., 1997). More recently, studies have reported reactivation in solid tumors as well, especially in breast cancer patients (Alexopoulos et al., 1999; Yeo

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et al., 2003). High HBV viral load before chemotherapy, Hbe ag positivity, male gender, young age, lymphoma or breast cancer as primary malignancy have been thought as probable risk factors for reactivation of Hepatitis B (Steinberg et al., 2000; Yeo et al., 2000). Over the past decade, it has been recognized that HBV reactivation risk during chemotherapy can be dismissed by the use of prophylactic lamuvidine.

The levels of HCV viral RNA has also been shown to increase while on chemotherapy in some case reports, however, case series review failed to find such complication common (Kanamori et al., 1992; Vento et al., 1996; Zuckerman et al., 1998). In a recent review it was reported that, after the rise by chemotherapy, upon the withdrawal of immunosuppressant, HCV RNA levels decrease with a concomitant rise in ALT levels which was explained by the suppression of immunity by chemotherapy and a rebound of reaction towards hepatitis C by its withdrawal (Hwang and Liang, 2010). However, unlike Hepatitis B, the impact of chronic HCV infection on patients undergoing chemotherapy is still not well defined.

In this study we aimed to determine the seroprevalence of Hepatitis B and C in patients with solid malignancies and also evaluate the follow up of liver functions in the seropositive group during chemotherapy, whether any reactivation has occurred or not.

Materials and Methods

The files of 990 patients with a diagnosis of solid malignancy, which were confirmed pathologically and were given adjuvant and/or palliative chemotherapy and still are on follow-up in the department of Medical Oncology at Kayseri Education and Research Hospital, were evaluated retrospectively. The cases that were found to have serologically determined hepatitis markers at diagnosis were included in the study. A total of 914 files were included in the study. Demographical properties of the patients and the primary sites of the malignancies were recorded. For the cases with HBV and/or HCV positivity, HBV DNA and HCV RNA levels, liver function tests at diagnosis and during follow-up and the treatment modalities that were chosen were determined.

Results

Of the 914 cases; 571 (62.5%) were female, 343 (37.5%) were male and the median age was 56. The most common types of cancer detected were breast carcinoma in 402 (43.9%), gastric in 116 (12.7%), colorectal in 102 (11.2%), lung in 73 (7.9%), genitourinary in 48 (5.3%) and renal cell carcinoma in 27 (2.9%) of the cases. The median number of chemotherapy cycles were 5 (range 4-8). Hbs Ag, Anti Hbs and Anti HCV positivity were detected in 40 (4.4%), 336 (36.8%) and 26 (2.8%) of the cases respectively. In the Hbs ag and Anti HCV seropositive patient group the most common cancer detected was breast carcinoma (14 and 12 cases respectively). In the Hbs ag positive group (n:40), 18 of them were shown to have detectable HBV DNA levels, while the rest 22 had negative HBV DNA levels. For all patients with Hbs ag positivity, prophylactic lamuvidine was administered a week before the start of chemotherapy till after the end of chemo, since all of them had adjuvant and/or palliative chemotherapy. During follow-up of these cases, liver function tests were all in acceptable levels. There were no interruptions in chemotherapy delivery because of hepatitis B and no side effect for lamuvidine was detected. Of these 18 HBV DNA positive cases, 2 cases with metastatic colon cancer having palliative chemotherapy together with lamuvidine, were shown to have HBV DNA negativity at the end of chemotherapy period.

In the Anti HCV positive group (n:26) 11 of them had detectable HCV RNA levels. One patient had been treated for HCV before the diagnosis of malignancy and his HCV RNA was negative from the start till the end of chemotherapy. Liver function tests of all the patients with HCV positivity were on regular follow-up and hepatic failure was not detected in any of them.

Discussion

Chemotherapy induced hepatitis reactivation may cause varying degrees of hepatic damage leading to disruption of chemotherapy and thereby compromising the cancer prognosis. So it is important to deal with the problem of hepatitis before the start of chemotherapy even in solid tumors to get the maximum benefit from chemotherapy.

In our study, HBs ag positivity was detected as 4.4% and Anti HCV positivity in 2.8% of patients with solid tumors. These are in concordance with the results in most of the studies from our country. Utkan et al. (2006) have reported that, in cancer patients the seropositivity of HBs ag and Anti HCV was 4.8% and 2.8% respectively. Kose et al (2011) examined hepatitis seroprevalence in 448 patients with solid malignancy and reported positivity of HBs ag in 4.2% and anti HCV positivity in 0.7% of them. They have found no significant association between types of cancers and HBs ag and Anti HCV positivity. In the study of Kose et al. (2011), the seroprevalence of Hepatitis C was slightly lower than our study results, whereas Uzun et al. (2002) have reported that the prevalence of Anti HCV was 6.7% among lung cancer patients, which was significantly higher compared to Turkish population and also to our study results. In our study, in 3 of 73 lung cancer patients HBs ag was positive but none had Anti HCV positivity detected.

In this study we also examined the effect of hepatitis B and C positivity during chemotherapy. In none of our patients with Hbs ag or Anti HCV positivity, liver failure or any delay in chemotherapy because of hepatitis was observed. In some of the patients, slight increases in transaminases were observed that were all below twice the upper normal limits and none had increases in bilirubin levels.

In the early reports, the effect of the antiviral agent lamuvidine was studied in Hbs ag positive patients who experienced ALT elevation attributable to HBV reactivation. They have concluded that this approach has a role in controlling HBV reactivation during

chemotherapy whereas still some fatal reactivations were also reported (Clark et al., 1998; Ter Borg et al., 1998; Cainelli et al., 2001). Later by serial monitoring of HBV DNA and ALT levels, it was shown that viral replication occurs 1-2 weeks before clinical picture of hepatitis occur in cancer patients receiving chemotherapy. Then a prophylactic strategy, as using lamuvidine before the start of chemotherapy for prevention of HBV reactivation and related morbidities and mortalities, has risen (Yeo and Johnson, 2006). The earlier reports about prophylactic lamuvidine were reported on hematological malignancies especially lymphoma patients. In the study of Persico et al (2002), 21 non-Hodgkin lymphoma patients with Hbs ag positivity were given chemotherapy and in 12 had hepatitis reaction, 9 of these were given lamuvidine and all were reported to recover. Another 3 patients were reported to have used lamuvidine from the beginning of chemo and they didn't have any hepatitis reaction. They concluded that lamuvidine was a useful drug to both treat and prevent HBV reactivation in patients with non Hodgkin lymphoma that receive chemotherapy.

Among solid tumors, the prevalence of hepatitis B and the effect of lamuvidine have been mostly studied in breast cancer patients. Yeo et al. (2004) in their retrospective trial, reported that prophylactic lamuvidine significantly reduced both the incidence of HBV reactivation from 31% to 6.5 % and also the disruption of chemotherapy. In a prospective and randomized trial on breast cancer patients, it was shown that there was significantly less HBV reactivation in the prophylactic lamuvidine receiving group compared with the group receiving lamuvidine only after proven HBV reactivation during chemotherapy (p 0.021). But the disruptions of chemotherapy and overall survival were the same for the two groups (Long et al., 2011). In a systematic review that contains 14 studies on both hematological and solid tumors, it was concluded that preventive lamuvidine reduced the risk of HBV reactivation by approximately 80% and that all patients testing Hbs ag positive should be considered for preventive lamuvidine before the start of chemotherapy (Loomba et al., 2008). But the optimal duration of lamuvidine treatment is still not crucial. In our study, prophylactic lamuvidine was started for all Hbs ag positive patients, one week before the start of chemotherapy and it was continued for 6 months after the completion of chemo. In these 40 patients there were no HBV reactivation or hepatitis flare detected and no lamuvidine related side effects were observed. Besides in two of our cases, HBV DNA was levels were found to be negative at the end of chemotherapy, with lamuvidine treatment.

Compared with hepatitis B, there is scanty data on management of Anti HCV positivity in cancer patients. The clinical impact of HCV infection on patients undergoing chemotherapy is not yet well characterized. There are conflicting evidence about the patients with HCV positivity and undergoing chemotherapy. Besides the studies that reported only mild-moderate elevations in liver enzymes of HCV positive patients with hematological malignancy undergoing chemotherapy (Zuckerman et al., 1998), in a recent review of 160 non-Hodgkin lymphoma patients with chronic hepatitis C, it was reported that 15% of them had significant liver toxicity (Arcaini et al., 2010). Also in diffuse large B-cell lymphoma patients, it was shown that, overall survival was significantly worse in the patients with chronic HCV infection than those without HCV infection (at a median follow up of two years overall survival rates were 56% and 80% respectively and p 0.02) (Besson et al., 2006). Still it seems that more studies are needed in this aspect. In our study we didn't detect any hepatic failure or delay of chemotherapy because of hepatitis, in HCV positive patients.

In conclusion, not only for hematological malignancies but also for solid tumors, screening for HBV and HCV is required before the start of chemotherapy. Prophylactic antiviral therapy for HBV reduces both the reactivation rates and HBV related mortality and morbidity. For HCV infection in patients receiving chemotherapy, uncertainty still exists.

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