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ORIGINAL ARTICLE

Non-Hodgkin lymphomas and carrier state of viral hepatitis B and C

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Summary

Purpose: To establish the characteristics and prognosis of newly diagnosed patients with non-Hodgkin lymphoma (NHL), who were carriers of hepatitis B (HBV) and C (HCV) viral infection.

Methods: 542 patients with NHL, diagnosed and treated in the University Hospital "Sv. Georgi", Plovdiv, were retrospectively analysed. Two NHL patient groups were created – the study group, consisting of 33 patients with NHL positive for HBV and HCV, and the control group, consisting of 40 randomly assigned patients with NHL and negative serology for hepatitis. Study and control groups were compared for basic characteristics and survival.

Results: The prevalence of hepatitis B surface antigen (HBsAg) among newly diagnosed patients was 5.72% and of HCV 1.84 %. Association with hepatitis viruses was more frequent in indolent than in aggressive NHLs (p=0.044). Liver dysfunction was registered more often in the study group (p=0.002). Reactivation of HBV infection was registered in 5 patients (12.19%) from the study group. There was no statistically significant difference between survival rate of patients in the study group and in the control group (p=0.738).

Conclusion: Hepatitis virus carrier state did not alter significantly the clinical course and disease prognosis (remission rates and survival) in our patient group. We recommend the routine testing for hepatitis infection in patients newly diagnosed with NHL in order to collect more data needed for the establishment of a possible causal relationship between hepatitis viruses and NHL. Since antiviral prophylaxis could positively impact the course of lymphoma treatment, national guidelines for the management of patients with hepatitis infection and NHL will prove to be necessary for the clinical practice.

Key words: hepatitis B, hepatitis C, non-Hodgkin lymphomas

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Introduction

It is considered that one quarter of malignant disorders have infectious etiology. The etiopathogenetic role of viruses has been recognized for the development in some carcinomas and sarcomas [1], e.g. HCV and hepatocellular carcinoma, EBV (Epstein-Barr virus) and nasopharyngeal carcinoma, HIV (human immunodeficiency virus) and Kaposi sarcoma, HPV (human papilloma virus) and uterine cervix carcinoma, and human herpes virus-8 and Kaposi sarcoma. There is fewer data on the role of viruses in the lymphomagenesis: EBV is isolated in 100% of the patients with Burkitt lymphoma; HTLV-1 (human T cell leukemia type I) and peripheral T-cell lymphoma; and HCV and mixed cryoglobulinemia (preneoplastic lymphoproliferative disorder).

The causal relationship between HBV and HCV infection and NHL lymphomas has been a subject of intense research for the past 20 years [2]. Most of the studies published have been conducted in regions with high incidence HCV infection and point to certain etiopathogenetic relationship between both diseases. However, the causality of lymphoproliferative disorders related to HCV and HBV carrier state remains uncertain. The predictive value of the virus carrier state related to the treatment outcomes (in terms of viral reactivation) as well as the necessity of antiviral prophylaxis haven't been established yet.

The purpose of this study was to analyse the characteristics and survival of patients newly diagnosed with NHL, who were carriers of HBV and HCV.

Methods

Patients

This retrospective study included 542 patients with newly diagnosed NHL, treated at the University Hospital "Sv. Georgi" – Plovdiv and the Comprehensive Oncology Centre – Plovdiv from 2008 to 2011. Positive hepatitis virus carrier state was registered in 41 NHL patients. For some of the patients no complete data were available for statistics.

We analysed the characteristics of two NHL patient groups – the study group, with 33 NHL patients positive for HBV and HCV, and the control group, with 40 randomly assigned patients with NHL and negative serology for hepatitis. Both groups were compared by main clinical parameters and survival. Clinical stage was defined according Ann-Arbor staging system. The therapeutic response was evaluated according to the International Working Group Response Criteria for NHLs.

Follow up

Patients in remission were followed at 3- to 6-month intervals in the outpatient department until April 2012 (end of the study). The median follow-up time was 18 months (range 1-143).

Statistics

Chi-square test and Student's t-test were used for comparison of both groups. Survival analysis was performed by the Kaplan-Meier method [3]. Comparison of survival curves was based on the log rank test. Survival time was measured from the date of diagnosis and endpoints were taken as death from all causes. Statistical analysis was carried out using the SPSS v.17.0 statistical package.

Results

The study group included 31 HBV (+) NHL and 10 HCV (+) NHL patients. Positive carrier state among newly diagnosed NHL patients was 5.72% for HBV and 1.84% for HCV.

Comparison of both groups

No statistically significant difference was found when the study and the control group were compared by demographic characteristics: age (t-test=1.28, p=0.202) and sex (x^2 =2.37,p=0.124), frequency of extranodal localization (x^2=0.025,p=0.874), complete remission rate (x^2=0.139, p=0.709) (Table 1).

There was a trend of diagnosing patients from both groups in advanced clinical stage (Table 1), and most stage IV patients belonged to the study group (Figure 1).

Viral hepatitis carrier state was found more frequently in indolent lymphomas (x^2=4.06, p=0.044) with significant difference between the study and control group (Figure 2).

Liver dysfunction was registered significantly more often in the study group (x^2=9.91, p=0.002; Figure 3).

Table 1. Characteristics of patients in the study and control group

Clinical parameters	*Study group (N=33) N %*		*Control group (N=40) N %*		*p-value*
Age, years (mean±SE)	59.5±1.81		63.5±2.01		NS
Sex					
Male	13	36.1	23	63.9	NS
Female	20	54.1	17	45.9	
Clinical stage					
Localized	10	40.0	15	60.0	NS
Generalized	23	47.9	25	52.1	
Remission rates (complete and partial)	19	46.3	22	53.7	NS
Extranodal localization	15	45.5	18	54.5	NS
Histological subtype					
Indolent	22	55.0	18	45.0	0.044
Agressive	10	31.3	22	68.7	
Liver dysfunction	11	33.3	2	5.0	0.002

NS: non significant

Survival

The mean survival time of patients in the study group was 54.6 months (95% CI 29.5-79.8). The survival of patients in the control group (42.6 months, 95% CI 24.1-61.1) was longer than that of study group, but without statistically significant difference (log rank=0.112, p=0.738; Figure 4).

Reactivation of viral hepatitis infection

Reactivation of HBV infection due to chemotherapy was registered in 5 patients (12.19%) from all hepatitis virus positive patients. In one patient reactivated viral infection in conjunction with chemotherapy ended in fatal outcome attributable to severe liver damage from the virus.

There were no cases of acute viral hepatitis infection in the control group.

Discussion

In the past 20 years a possible causal relationship between the viruses of infectious hepatitis and NHL has been proposed in the literature, most of the studies pointing to a relationship between HCV and NHL [2,4]. A meta-analysis of 15 case-control studies and 3 prospective studies (9 of which had not been included in previous meta-analyses) found an increased relative risk of developing NHL among HCV-positive subjects, irrespective of histological subtype [5]. Evidence for causality is the successful achievement of complete remission in some cases of indolent lymphoma solely with the administration of antiviral therapy [6]. Data on the role of HBV in lymphomagenesis is scarce and controversial. A 14-year follow-up of HBV (+) subjects also determined an increased risk of NHL, but only in certain subtypes [7].

The reported frequency of HBV and HCV carrier state among newly diagnosed patients with NHL in our study is consistent with the current literature data: 1.89-2.8% prevalence of HCV and 3.7-23.5% of HBV [8-10]. Frequencies vary, depending on the infectious rates of the population in a certain region. Our data corresponds with published data for the Black Sea region [11]. On the other hand, the reported frequency of HBV and HCV among patients with NHL in our study was higher than the rate of healthy population in the Plovdiv region (3.8% for HBV and 1.3% for HCV), which could be suggestive of a possible causal relationship [12]. Published data suggests a possible etiopathogenetic relation between hepatitis viruses and certain NHL subtypes [13]. Some authors indicate higher frequency of the association of aggressive NHL subtypes with viral hepatitis carrier state [4,8]. Others find higher incidence of indolent lymphomas (M. Waldenström) among HCV carriers [9]. Suppos-

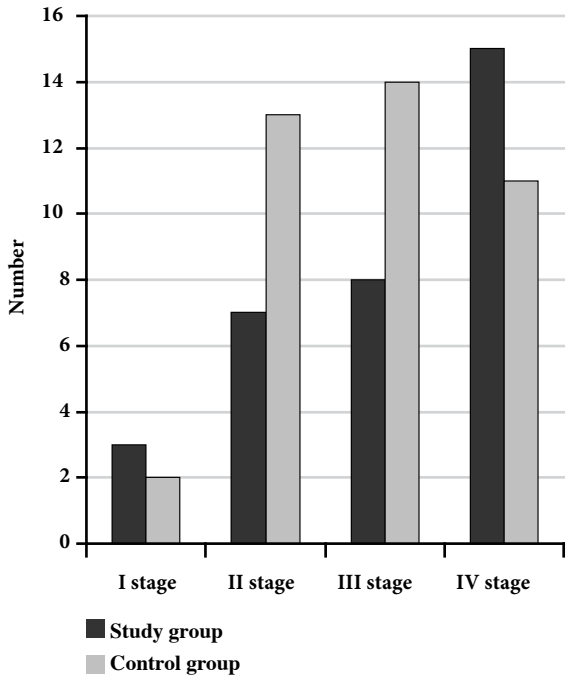

Figure 1. Patient distribution according to clinical stage in the study and control groups (p>0.05)

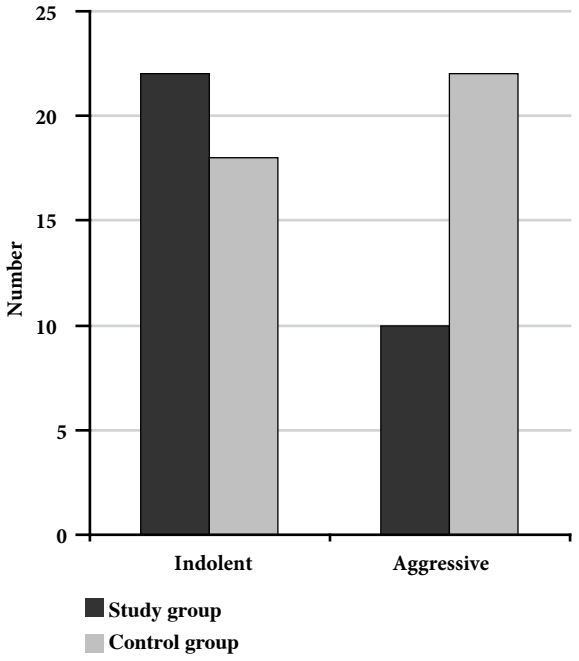

Figure 2. Patient distribution according to histological type (p=0.044).

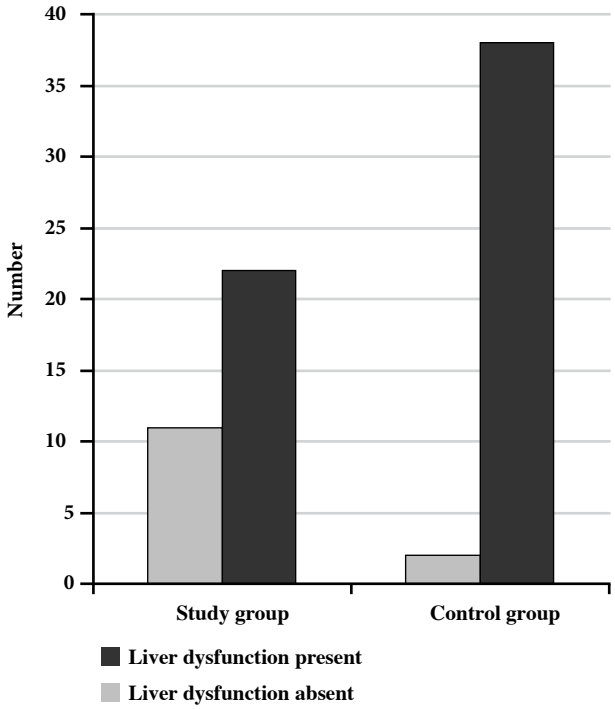

Figure 3. Patient distribution according to the presence of liver dysfunction (p=0.002).

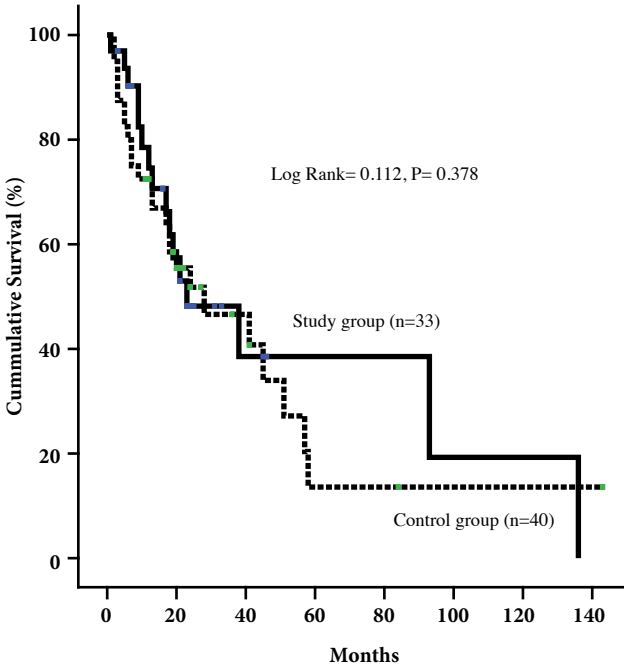

Figure 4. Survival of NHL patients from the study and control groups.

edly, higher prevalence of HCV is found in aggressive diffuse large B-cell lymphomas (DLBCL) after transformation from indolent NHL. In our study we found more frequent association of hepatitis viruses with indolent lymphomas, which could be supportive of the latter statement.

Viral infections confer certain risk for developing NHL, mostly due to causing primary or secondary immune deficiency. Unlike known oncogenic viruses and while it is typical for HBV DNA, hepatitis C RNA does not integrate within the host's genome. Possible mechanisms of HCV involvement in lymphomagenesis are currently being discussed in the literature. A direct role of HCV and its presence in hematopoietic cells is questionable. Most authors support the concept of chronic B-cell stimulation by viral antigens, leading to polyclonal B-cell expansion, immune dysregulation and thus to B-cell malignant lymphoroliferative disorder. Triggering mechanism is the binding of E2-protein from the viral envelope to the B-cell surface complex CD19/CD21/CD81, followed by clonal activation and chronic B-cell proliferation [2].

Data on the prognosis of patients with NHL, infected with HBV and HCV is controversial as well. High percentage of viral reactivation (60%) in HBV (+) patients due to immune suppression has been reported in the literature [15-17]. This risk persists up to 6 months after chemotherapy cessation. According to other data 22.3 % of NHL patients develop acute hepatitis while on chemotherapy with mortality rate of 3.7% [18-20]. Some major centers such as the Memorial Sloan Kettering Cancer Centre – USA have adopted routine antiviral prophylaxis against HBV infection in NHL patients at least 6 months following completion of chemotherapy. Most frequently used antiviral agents are Lamivudine, Entecavir, Temofovir and others.

Our patients did not receive antiviral prophylaxis. We registered a rather low frequency of viral reactivation during chemotherapy (12.19%) and one lethal case associated with viral reactivation and fulminant liver damage. This prompts the expectation of a positive impact of antiviral prophylaxis during the course of lymphoma treatment and urges the necessity of pharmaco-economic analysis.

Conclusion

In this study we determined an infectious rate of 5.72% for HBV and 1.84% for HCV among patients newly diagnosed with NHL. Hepatitis virus carrier state seems not to affect significantly the clinical course and prognosis of NHL. We recommend the routine testing for hepatitis infection in patients with newly diagnosed NHL in order to collect more data needed for the establishment of possible causality. Since antiviral prophylaxis could positively impact the course of lymphoma treatment, national guidelines for the management of patients with hepatitis infection and NHL will prove to be necessary for the clinical practice.

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