

AN OVERVIEW OF THE INFLUENCE OF EBV ON THE OUTCOME OF PEDIATRIC PATIENTS WITH NEOPLASIA IN ONE CENTER EXPERIENCE

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Abstract

Rationale. We live in a world in which we are surrounded by many organisms which influence our life. A good example is the Epstein Barr virus (EBV) which is spread worldwide, infecting over 90% of the adult general population. The tumoral range in which EBV is incriminated is large and with prospects to be modified: Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma etc.

Objective. In this paper we report the experience of one pediatric cancer center regarding the influence of the Epstein Barr virus on the outcome of the neoplasia.

Methods and Results. A retrospective consecutive study of 5 years, 2005-2010, included the clinical data, histology, stage of the disease, titer of specific antibodies for EBV, serological and imaging evaluations of the patients treated.

For our population of 35 patients, based on the data and their statistical analysis we identified a cut off value of IgG anti VCA significant for the response to chemotherapy.

Discussion. There are few data concerning the influence of EBV regarding the outcome of pediatric neoplasia. The published studies suggest a positive influence of EBV especially in Hodgkin's disease mixed cellular subtype. In this study we identified a cut off value for IgG anti VCA antibody with statistical significance for the prognosis of the response to treatment.

Keywords: Epstein Barr virus, malignancy, prognostic factor.

STUDIUL INFLUENȚEI VEB ASUPRA PROGNOSTICULUI CANCERELOR PEDIATRICE ÎNTR-UN CENTRU ONCOLOGIC

Rezumat

Scopul studiului. Trăim într-o lume în care suntem înconjurați de o multitudine de microorganisme care sunt strâns legate de viața noastră. Un bun exemplu este reprezentat de virusul Epstein Barr (EBV), care este extrem de răspândit la nivel mondial, peste 90% din populația adultă fiind infectată. Spectrul tumoral în care este implicat este larg și în continuă schimbare: limfom Burkitt, limfom Hodgkin, carcinom nazofaringian etc.

În acest articol se încearcă exemplificarea experienței unui centru implicat în tratamentul cancerelor pediatrie, în ceea ce privește influența EBV în evoluția bolii neoplazice.

Metodă și rezultate. Au fost luate în studiu, în manieră retrospectivă consecutivă, pe o perioadă de 5 ani, datele clinice privind histologia, stadiul tumoral, titrul de anticorpi specifici EBV, evaluările serologice și imagistice ale pacienților tratați.

La lotul luat în studiu, de 35 de pacienți, au fost studiate multe item-uri detaliate în articol, statistic semnificativă fiind o valoare cut off pentru IgG anti VCA pentru

răspunsul la chimioterapie.

Concluzie. Sunt puține date privind influența EBV față de prognosticul neoplaziei în pediatrie. Studiile publicate sugerează, mai ales în limfomul Hodgkin cu celularitate mixtă, un rol pozitiv. Studiul de față a identificat o valoare cut off statistic semnificativă ce poate fi un factor prognostic la răspunsul la tratament.

Cuvinte cheie: Epstein Barr, malignitate, factor de prognostic.

INTRODUCTION

We live in a world in which we are surrounded by many organisms which influence our life. A good example is the Epstein Barr virus (EBV) which is spread worldwide, infecting over 90% of the adult general population [1]. The tumoral range in which EBV is incriminated is large and with prospects to be modified: Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma etc.

It is well known that the etiology of cancer is multifactorial, one of the possible causes being infectious – MALT lymphoma – Helicobacter pylori, cervical cancer – papillomavirus, hepatocarcinoma – B or C hepatic virus, Kaposi sarcoma – herpetic virus etc.

EBV is a virus in the Herpesviridae family identified in 1964 in a Burkitt cell line [2] and after many years of research WHO declared EBV to be first class carcinogen [3].

AIM OF THE STUDY

Investigation of the role and prognostic importance of EBV in a well-documented series of classical Hodgkin's and non-Hodgkin's lymphoma in patients treated at a single center in Romania.

PATIENTS AND METHODS

In a retrospective study we included patients treated in National Institute of Oncology Cluj Napoca between 2005 and 2010. Our group consisted of 35 patients with malignant Hodgkin or non-Hodgkin lymphoma. From their clinical records we extracted clinical data, including patient demographics, hematology, erythrocyte sedimentation rate, albumin, lactic dehydrogenase level, clinical stage of the disease, positivity of B signs, bulky disease (> 10 cm or mediastinal mass exceeding one third of the thoracic diameter) and we calculated the International Prognostic Scores (IPI), type of treatment, response to treatment. All the histology data were reviewed in order to ensure a consistent diagnosis of the patients with clinical files. Inclusion criteria were: histological evidence of malignant lymphoma, age between 1-18 years, treated by standard chemotherapy, EBV infection confirmed by positivity of IgG anti VCA. We excluded the patients unable to finish the chemotherapy or with incomplete clinical data or EBV negative. In our group we had 8 girls and 27

boys, with a median of age of 12 years. Median follow-up was 27 months (3.3-60 months). All were treated with chemotherapy according to the best available international recommendation for chemotherapy regimen.

As previously mentioned we studied the statistical influence (if any) of the presence of EBV certified by the positivity of IgG VCA antibody on the clinical outcome of the patients. We used the statistical procedures adequate for the aim of this paper, descriptive or inferential techniques. Differences for patients and disease characteristics between EBV-IgG VCA high level and EBV-IgG VCA low level cases were compared using either chi-square test or Fisher's exact test. We used the SPSS 17.0 statistical program, Medcalc 8.3.1.1 or Microsoft Office – Excel 2007 facilities.

First query: do we have a significant influence of the level of EBV infection on the patient's chance of cure? In order to respond to this question we performed a statistical analysis: regression curve which identified a cut off of IgG VCA antibodies at 213,44 UI/ml statistical significant for patient response to treatment.

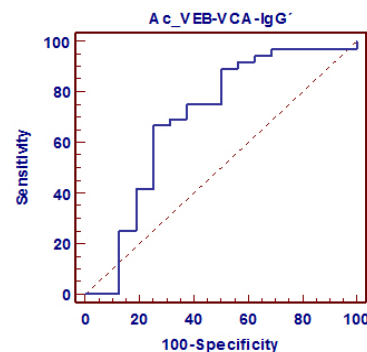


Fig. 1. ROC curve for IgGVCA level for response to therapy.

Starting with this value of IgG VCA we analyzed if it was statistically significant for the patient's response.

The chemotherapeutic response, gender and type of lymphoma are listed in the following table:

Table I. The main patient's characteristics.

Patients	IgG VCA < 213.4	IgG VCA > 213.4	p value
Complete responders (CR)	9	17	0.007
< CR	8	1	
Female gender	4	4	1.000
Male	13	14	
Hodgkin lymphoma	6	9	0.380
Non-Hodgkin lymphoma	9	9	

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Statistical correlations were only found with high level of IgG VCA. The chance to have a complete response to chemotherapy was double in the subgroup of high IgG VCA level (17/26) compared to lower level (9/26).

Table II. Statistical analysis within histological subgroups regarding the 2 levels of IgG VCA.

Patients	IgG VCA < 213.4	IgG VCA > 213.4	p value
Histological subtypes NHL			
Burkitt	6	8	0.276
Large B cell	2	1	
T cell	2	0	
Histological subtypes HL			
Nodular sclerosis	4	3	0.582
Mixed cellular	1	3	
Lymphoid depletion	1	2	
Lymphocytic reach	0	1	

Investigating whether EBV influenced or not the median age and tumor's marker LDH or median larger tumor diameter the p value was not significant ($p=0.239$). No difference was noted regarding the presence of B signs between the two levels of IgG VCA.

Through the treatment period, the presence of an infection with EBV in high levels did not influence the hematological toxicities (all three lines – p values not significant). The clinical stage of the patients in the presence of EBV was not significantly higher than those with reduced levels of IgG VCA ($p=0.485$) and did not involve internal viscera more frequently ($p=0.592$).

DISCUSSION

The presence of EBV in patients with HD or non-HD is variable. The published studies have shown a geographical variation: Asian population appear to have a low frequency of HD with intermediary level of EBV [5].

The published data regarding the influence of the infection with EBV on the general outcome in pediatric malignancies are controversial and with unknown dimension. The present paper has tried to offer a general view in one well known oncological center. The incidence of intense EBV infection (interpreted as high level of IgG VCA) is approximately 50% (17/35 patients included). No difference on disease free survival or overall survival was evidenced depending on titer of IgG VCA. The only chance to reach complete response depended significantly on IgG VCA high level, which was more frequently associated with a complete response at the end of treatment ($p=0.007$). The high rate of intense infection with EBV is discordant to existing data in developed countries [6,7]. Higher rates are frequent in low income countries [8]. For the time being we do not have a well-documented explanation for these differences.

The latest data suggest a positive role for EBV in the history of Hodgkin disease. In a positive trial published – Montalban [9] – better overall survival and higher rate of complete response in EBV-positive patients was found. Despite the fact that we did not evidence a survival advantage, the higher rate of complete response demonstrated in our population is in agreement with these findings. Unfortunately due to insufficient number of patients an analysis of histological subtypes and level of IgG VCA did not offer a statistical significance. The presence of EBV did not emphasize the hematological toxicities secondary to chemotherapy regimen in our study. Male sex seems to be more frequently affected by HD or non – HD regardless of intensity of EBV infection, as reported in literature [10].

In conclusion our study has revealed the interesting fact that the intense infection with EBV (high titer of IgG VCA) seems to be related with increased chance of complete response after chemotherapy. Boys seem to be more often affected regardless of intensity of EBV infection. No histological subtype or stage or LDH level linked statistically to EBV exposure. An extended analysis is ongoing.

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