

DOCTORAL (Ph.D.) THESIS

ETIOLOGICAL AND CLINICAL STUDIES IN
HODGKIN'S-LYMPHOMA

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INTRODUCTION

Hodgkin's-lymphoma (HL) is a malignant disease, in Hungary 160-200 new cases are diagnosed a year.

Although the origin of HL tumour cells is already known (they originate from germinal centre B cells), the cause of HL has still not been cleared. It is supposed that both endogenous (genetic and immunologic) and environmental factors contribute to its development. The role of infection in the etiology of HL has been questioned since its first description; it was not by chance that they called it Hodgkin's disease (HD) as the malignant or infectious nature of the disease had not been known for a long time. Substantial etiologic proofs have been found only for Epstein-Barr-virus (EBV) infection though HL patients in regions with different socio-economic development show different prevalence of EBV positivity. In EBV negative cases, besides the „hit and run mechanism” other viruses are supposed to have an etiological role in HL. Besides herpes viruses, more attention has been paid to hepatitis viruses since among these hepatitis C (HCV) and G (HGV) viruses have a lymphotropic nature.

Cellular immunodeficiency has long been known to be present in HL patients. It can be detected at early stage but may worsen with the progress of the disease. Some believe that cellular immunodeficiency is present before the onset of the disease and may have a role in the development of HL.

HL differs from other oncohematologic diseases for various reasons. HL was the first disease where the efficacy of polychemotherapy had been proven. HL is primarily the disease of people of working age so its social importance overgrows its prevalence. Unlike in other hematologic or solid tumours, in HL malignant Hodgkin, Reed-Sternberg (HRS) cells and variants are present in the tumorous tissue only in 1-2%. The majority of the tumorous mass are composed of surrounding reactive cells (B and T lymphocytes, eosinophils, plasma, mast and neutrophil cells) stroma cells and connective tissue. Nowadays, unlike from other oncohematologic diseases, 80% of HL patients recover or achieve long term survival but it is also known that there are substantial differences in the chance for survival among the patients. Besides disease involvement and stage, the therapeutic efficacy is influenced by several factors. Newer and newer prognostic factors are being searched for in the literature to supplement existing ones. The followup of patients has revealed that late complications of the treatment are frequent, they substantially decrease long time survival and the quality of life of the patients. Nowadays,

the treatment of choice is a patient-oriented, risk-adapted therapy with the aim of treating more patients while decreasing late complications. The improvement of diagnostic methods, the possibilities of stage- and prognosis-adapted treatment as well as the use of supportive therapy have substantially increased the chances of survival and recovery of our HL patients. The treatment and followup of HL patients started at our department at the beginning of 1970-es. I joined the team in 2000. HL is the success story of haematology, we have learnt a lot during the past decade. If we want to improve our results, we need to know about the experiences of other work teams as regards to treatment, patients' characteristics, prognostic factors, follow up of early and late complications and published data.

AIMS

The following aims were set during the study of patients treated and followed up at our department:

1. Study of EBV association and search for any relationship between EBV positivity and clinical, therapeutic, survival parameters of the patients.
2. Evaluation of HCV and HGV positivity and comparison to clinical, therapeutic data of HL patients.
3. Analysis of permanent immunological alterations of HL patients in long time remission or recovery. Comparison of *Helicobacter pylori* (HP) infection of HL patients and that of healthy controls. Search for any difference between the prevalence and virulence of HP infection in HL patients and in healthy population in relation to the immunological alterations. Search for any differences between HP positive and negative HL patients as regards to clinical, therapeutic data and immunologic parameters.
4. Retrospective analysis of the prognostic role of tissue eosinophilia and mastocytosis in the lymph nodes of HL patients.
5. Analysis of the clinical characteristics, therapeutic and survival results of HL patients with mediastinal bulky tumour (MBT). Study of the usability of 18F-deoxy-D-glucose (FDG)- positron emission tomography (PET) in clinical practice for mediastinal residue in uncertain complete remission (CRu).
6. It was our aim to evaluate the presence of second malignant tumour (SMT) and find any relationship as regards to the treatment employed and plan future treatment protocols for both the treatment and the followup of HL patients.

PATIENTS AND METHODS

1. Patients

Data on patients treated at the 3rd Department of Medicine between 1970 and 2004 were analysed. Data collection was done using all available material (case records, clinical and pathological final reports, Medsolution database).

HL diagnosis was ensured by histopathologic samples taken from the appropriate tissue in each case, histologic subtypes were categorised according to Lukes and Butler's criteria and REAL classification. The definition of the extension of the disease was based on clinical examinations, the Ann-Arbor principles and their Cotswolds modification. Treatment was always done according to the protocols in use. Treatment groups were as follows: only radiotherapy (RT), only chemotherapy (CT), combined radio-, chemotherapy (CMT). Therapeutic responses: complete remission (CR), partial remission (PR), non reacting (NR) were categorised according to the WHO recommendations.

2. Methods

EBV association in HL and its effect on therapeutic results and survival

The analysis was done using formalin-fixed, paraffin-embedded histologic samples.

1. Immunohistochemical (IHC) examinations: revision of histologic samples of HL patients in accordance with the WHO recommendations using CD15, CD20, CD30, CD45, EMA, BCL-6, ALK1 monoclonal antibodies.

Detection of latent membrane protein (LMP)1, EBV nuclear antigen (EBNA)2 proteins by monoclonal antibodies produced in mice (DAKO).

2. In situ hybridisation (ISH): EBV encoded RNA (EBER) was detected using EBV oligonucleotide kit (Novo-Castra) following the manufacturer's instructions.

3. DNA-isolation and polymerase chain reaction (PCR): DNA intactness was controlled by the amplification of a 210 bp section of human β -globin gene. For PCR analysis to detect EBV only β -globin-positive samples were used. For EBV detection a 171 bp section of BamHI-W fragment large internal repeat region of the virus was amplified. For the detection of the virus, touchdown, hotstart PCR technique was employed. As a positive control, EBV-infected DNA isolated from B95-8 lymphoblastoid cell line was used.

Analysis of HCV, HGV infections in our patients

HCV-, HGV were detected by nested PCR in the Virus Nucleic Acid Laboratory of the National Health Centre and in Johan Bela National Epidemiologic Centre. The presence of HbsAg was examined by enzyme-linked immunosorbent assay (ELISA) from blood.

Immunologic alterations, Helicobacter pylori infections in HL patients

Samples were taken from heparin-anticoagulated blood.

1. Determination of lymphocyte subpopulations was based on cell surface CD markers using fluorescence dye conjugated monoclonal antibodies. The samples were processed according to the Coulter QPREP protocol and evaluated by Coulter EPICS-XL-4 flow cytometry.
2. Determination of intracytoplasmatic cytokine in CD4+, CD8+ cells was done by Coulter EPICS-XL-4 flow cytometry.
3. Measurement of soluble cytokines was done by ELISA.

Analysis of Helicobacter pylori infection:

For the detection of fresh HP infection ¹³C urea breath test was used (BreathMAT™, Finnigan).

Chronic HP infection was confirmed by the detection of anti HP IgG and IgA using ELISA (Dia. Pro Diagnostic Bioprobes).

Anti cytotoxin-associated protein (Cag)A IgA- and IgG isotype antibodies were detected by ELISA.

Retrospective study of the prognostic importance of eosinophil and mast cells in HL-patients' tissue samples

Eosinophilia percentage was examined in paraffin-embedded haematoxylin eosin dyed samples at the Department of Pathology in 5 randomly selected high resolution vision fields. The quantity of eosinophil cells was given in the percentage of all the cells seen in 1 vision field, then it was averaged for the 5 vision fields. Two groups were made. Group 1: mean ratio of eosinophil cells among the reactive cells was under 5%, the sample was considered negative for eosinophil infiltration. Group 2: mean ratio of eosinophil cells was $\geq 5\%$ eosinophilia was considered. The detection of mast cells was done in paraffin-embedded tissue samples using mast cell specific anti tryptase monoclonal antibodies by IHC. Similarly to eosinophilia, tissue mastocytosis was considered if mast cell ratio was $\geq 5\%$.

Mediastinal bulky tumour and experiences with FDG-PET

MBT, CRu were stated according to the Cotswolds modifications.

PET examinations were carried out at the PET Centre using GE 4096 Plus whole body PET camera manufactured by General Electric. A mean dose (80 μ Ci-2,96 MBq of FDG/kg body weight) of positron emission FDG of $5,4\pm 2,4$ mCi (200 ± 89 MBq) was employed. In the case of farmacon cumulation that could not be considered as focal or physiological variants, the tumour/background (TBR) served as the basis for decision. The appropriate area of the opposite side was considered as background if it was not involved or the surrounding soft parts situated approximately in the same depth. The results yielded 3 groups: negative by FDG-PET, $TBR > 3$ tumour positive and $TBR \leq 3$ uncertain positive. Strict followup of patients with negative and uncertain positive PET results was based on physical examinations, laboratory and imaging methods. In PET positive cases – if several, independent areas were involved – the patients received further treatment. If only one region was PET positive, histological examination was performed for confirmation.

Second malignant tumour in patients treated for HL

The diagnosis of SMT was based on clinical and histological examinations. Skin cancer was not studied in SMT.

Survival was determined by Kaplan-Meyer's method.

In the statistical analyses (χ^2 , Mann-Whitney-test, Fischer exact test, multivariate analysis, log-rank test), $p < 0,05$ probability level was considered significant. For the analyses SPSS 13 Statistics program was used.

RESULTS, CONCLUSIONS

EBV association in HL and its effect on therapeutic results and survival

Out of 109 HL patients (45 females, 64 males) 47 (43%) were LMP1 positive, there was no EBNA2 positivity so the samples belonged to latency type II. Each of the LMP1 samples was positive by PCR. The detection of EBER was performed in the tissue samples of 41 patients, 18 (44%) were positive. Out of the 23 negative samples 4 became positive by PCR, there was no LMP1 positivity. The difference is explained by the higher sensitivity of PCR. At the same time, PCR - unlike IHC and ISH – is not suitable for the differentiation of positive environmental reactive cells from HRS cells. The clinical, therapeutic data and response to treatment of EBV positives (LMP1 positivity) and negatives did not differ significantly. Overall and event free survival rate was somewhat more favourable in EBV negatives but no significant differences were found. Our data show that EBV association of the patients studied in the north-eastern part of Hungary is characteristic of moderately industrial countries. On considering HL and EBV association disease models, our patients could not be categorised to either of them, the characteristic disease groups were, however, more or less represented, which can be explained by the differences in the economic development, industrialization and living standards in the country.

Analysis of HCV, HGV infections in our patients

Out of 111 HL patients HCV was confirmed by nested PCR in 10 cases (9%), HGV in 9 cases (8,1%) and out of these HCV and HGV coinfection in 2 cases (1,8%), by ELISA 1 patient (0,9%) was HBV infected. When compared to data on Hungarian blood donors, HGV positivity was 1,5 times more frequent but HCV positivity showed a tenfold increase in our patients with HL, the prevalence of HBV infection did not differ. No alterations were found in the clinical and therapeutic characteristics of hepatitis virus positive and negative patients. The few data found in the literature are also contradictory as regards to the relationship of HL and HCV, HGV, our data are suggestive only of the etiological role of HCV but no definite conclusions can be drawn.

Immunologic alterations, Helicobacter pylori infection in our HL-patients

127 HL patients in complete remission for at least 2 years were included in the study. In HL patients, CD3+, CD4+ cell percentage significantly decreased in peripheral

blood while CD8+, CD19+, CD56+ cell percentage and late activated CD3+/HLADR+ T cell percentage showed a significant increase as compared to the control group. In HL, IL-4 expression – with the exception of Tc2 cells – significantly decreased. IL-10 expression was significantly elevated both in CD4+ and CD8+ cells in HL. As regards to soluble cytokine in HL, IFN- γ level showed a significant decrease in peripheral blood while IL-10 was significantly elevated. We believe that this is indicative of a permanent immunosuppressive stage which can be seen in patients who recovered from the disease or have been in complete remission for a long time. It may also have been present before the onset of HL and might play a role in the development of HL.

Out of 127 HL patients 45 (35%) were HP positive by ^{13}C urea breath test, out of the 60 healthy controls 25 (42%), there was no notable difference between the 2 groups. No significant differences were found either as regards to HP infection detected by serologic examination and virulence factor expression. No notable differences were found in the clinical and therapeutic data of HP positive and negative patients. In HP positive HL patients besides significantly increased CD8+/IL-10 production and elevated CD3+/HLADR+ percentage cell ratio, a decreased ratio of CD14+/CD16+ expression were noted. The reason for the increase in CD3+/HLADR+ cell percentage is usually infection, among them HP infection. The decrease in CD14+/CD16+ cell percentage may be related to the inhibitory effect of HP infection on monocyte proliferation. The increased IL-10 production of CD8+ cells may also be due to HP infection but its mechanism is not known today.

Retrospective study of the prognostic importance of eosinophil and mast cells in HL-patients' tissue samples

Out of 104 HL patients (50 females, 54 males) tissue eosinophilia was found in 62% of the patients, mastocytosis in 75%. On comparing the clinical data on eosinophil and mast cell positives and negatives, no significant alterations were found. Both general (OS) and event free survival (EFS) were the most favourable with tissue eosinophilia and mast cell negatives. On analysing the complex effect of tissue eosinophilia and mast cell infiltration, survival parameters (OS, EFS) were the most favourable for eosinophil and mast cell negatives, though significant differences could not be shown in either case. However, based on the prognostic factors for OS and EFS used in clinical practice today we found significantly better OS in patients with favourable prognosis than in patients with unfavourable prognosis, and significantly better EFS and OS parameters in the IPS 0-3

patient group than $IPS \geq 4$. Literary data are contradictory as regards to the role of tissue eosinophilia and studies on mast cell infiltration are scarce. Our experiences suggest that the prognostic strength of tissue eosinophilia and mastocytosis (or the two together) do not provide any advantage for clinical practice. To solve this problem, further studies involving a great number of HL patients should be carried out.

Mediastinal bulky tumour and experiences with FDG-PET

Out of 193 HL patients 42 (22%) had MBT. The patients with MBT were diagnosed in a greater percentage at early stage of the disease and were younger. As regards to histologic subtypes, there were no LP and NLP among them. The treatment employed was almost the same since 100% of the MBT patients received combined therapy (CMT). Comparatively more MBT patients received high dose therapy (HDT) and autologous haematopoietic transplantation (AHSCT). Unlike in earlier decades, the parameters for the chances of recovery (OS, relapse free survival (RFS)) in MBT patients were not worse than those without MBT, which can be explained by lower mean age, more favourable tumour stage and CMT. CMT, however, as well as the greater number of HDT, AHSCT, PET examinations made the treatment of MBT patients a bit more expensive. It should be noted that late effects of CMT may appear years and decades later and will effect long time survival.

The prevalence of post treatment intrathoracal residue is 20% in HL patients, which makes it difficult to decide on the necessity of a new treatment. FDG-PET examination for patients with MBT was indicated in all cases due to post-treatment mediastinal residues. In patients without MBT, mediastinal or residues at other sites were indicated. 8 of our MBT patients had 11 FDG-PET examinations and 19 patients without MBT had 20 examinations. Out of the 4 positive MBT cases 1 was false positive, out of the 8 positive cases without MBT 2 were false positive. Out of the 6 MBT patients with negative FDG-PET examinations 1 relapsed 23 months later. Out of the 11 patients without MBT with negative FDG-PET results 1 relapsed 14 months later. In the two groups the patients remained in remission after a total of two uncertain positive results. Our experiences and literary data confirm that negative PET examinations ensure in 100% that no progress or relapse will occur for at least a year. The predictive value of positive examinations is, however, influenced by several factors, such as inflammation, infection, the period of time between end of treatment and PET and several other factors that are not known today.

Second malignant tumour in patients treated for HL

Data on 470 patients were evaluated. The mean followup time was 10,2 years (9 months-33 years). SMT was found in 34 cases (7,2%), solid neoplasms in 26 cases (5,5%), hematologic malignancy in 8 cases (1,7%). Bronchopulmonary tumour was the most frequent in the first group and non-Hodgkin lymphoma (NHL) in the latter. In hematologic malignancies, the patients were usually older at HL diagnosis than those with solid tumours. The mean age of patients with solid tumour at HL diagnosis was 38,1 years (18-59 years), in later hematologic malignancies 45 years (17-64 years). Latency time before the appearance of hematologic malignancies was 3,3 years (9 months-12 years), a shorter period of time than in solid neoplasms, on the average 13,5 years (1-33 years). Though no significant relationship was found between HL treatment and SMT, it is to be noted that tumours, out of the 20 chemotherapy (ChT) treatments 17, and in late hematologic tumours out of 8 ChT treatments 6 patients were given treatment containing alkaline neoplastic agents (CV(O)PP and variants). During the follow up of HL patients, attention should be paid on the detection of SMT on time. Following the treatment protocols used in clinical practice today (discarding alkylates, involved field irradiation instead of extended field, lower radiation dosage), the prevalence of SMT is expected to decrease.

SUMMARY - CONCLUSIONS

1. EBV infection may play a role in the development of HL in Hungary since it can be detected in 50% of the patients. EBV positivity is more frequent in men and in mixed cellularity histologic subtype. Our patients could not be categorised to any of the HL-EBV association disease models but some disease groups were more or less represented. The treatment and survival results of EBV associated HL patients did not differ significantly from those without the infection.
2. The role of HGV in the aetiology of HL in Hungary is not probable, HCV as an etiologic factor cannot be excluded.
3. As regards to immunological alterations, we found IL-10, TGF- β overproduction in HL, which may be one of the etiologic factors of HL. The prevalence and virulence of Helicobacter pylori infection in HL did not differ from that of the healthy control group. The increase in CD3+/HLADR+ cell percentage and CD8+ cell IL-10 expression in HP positive HL patients as well as the decrease in CD14+/CD16+ monocyte percentage might have been the result of HP infection.
4. We did not find any prognostic role for examination of eosinophil and mast cells in the histologic samples of HL patients and we believe it does not mean any advantage in clinical practice. To solve this question, complex studies involving a great number of HL patients should be carried out.
5. We have confirmed that with the use of CMT, the therapeutic and survival results of patients with mediastinal bulky tumour do not differ significantly from those of other HL patients. We have proven that FDG-PET examinations are suitable for the evaluation of the viability of post treatment residual tumour tissue in HL patients and thus may help in selecting further therapies
6. We have shown that the second malignant tumour is not an infrequent treatment complication, its prevalence is 8%, the most frequent solid tumour is lung cancer and most frequent hematologic malignancy is NHL. Solid neoplasms may appear long, even after decades after treatment. Attention should be paid to their early diagnosis during followup and applying the treatment protocols today in use in clinical practice, they prevalence is expected to decrease.

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