E14. **ACTUALITIES CONCERNING HODGKIN'S LYMPHOMA.**

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Introduction: Hodgkin's lymphoma is a malignant limfoproliferation in which Reed Sternberg cells are in a reactive inflammatory environment. The incidence of lymphoma is approximately 5/100,000 inhabitants/year (1) and represents about 1% of cancer cases that occur annually (2). Its incidence varies according to gender, age, geographic location, ethnic group and socioeconomic status (3). In developing countries the incidence depending of age is bimodal: prevail in the 3rd and 8th decade of life. The second peak may be due to the confusion with other clinical cases of lymphoproliferations which it resembles with (4). In young people, the incidence is equal between the genders (1). The disease occurs more often during the months of February and March. The highest rates of mortality due to it are recorded in countries where the incidence of lymphoma is the smallest and vice versa (3). Classic Hodgkin's lymphoma has a particular histology, meaning that few lymphoma cells (less than 1% of the lymph node cell population) are surrounded by numerous inflammatory cells. It is considered that, in the affected lymph nodes, the interaction between stromal cells and reactive nonmalignant cells with Reed Sternberg cells plays an important role in the pathogenesis of the disease. The present inflammatory cells have an abnormal activity: there is an expansion of myeloid suppressor cells, a signaling dysregulation through regulatory T cells and HLA-G protein and a malfunction of the natural killer cells, which may have prognostic role (5). Hodgkin and Reed Sternberg cells would have originated in the germinal center cells (GC) centers or lymphocytes B post-GC, because they are carrying the mutated gene coding the variable region of immunglobulin (6).

Ethiopathogenesis: The possible role of infection with Epstein-Barr virus in the pathogenesis of this lymphoma is discussed, through long-lasting antigenic stimulation (at 40-60% of patients Sternberg-Reed cells are latent infected with Epstein Barr virus). It is believed that the virus may have a central pathogenic role, in an initial event, when B cells from GC affected by apoptosis would be saved (5). A genetic signature associated with Epstein-Barr virus status in the histopathological lymph node sections seems to be characteristic of TH1 antiviral immune response. Sustained activation of NF-kappaB supported is responsible for the proliferation of Hodgkin and Reed Sternberg cells and prevents their entrance into apoptosis. TNFAIP3 gene encodes a natural inhibitor of NF-kappaB (called A20). Cells bearing the TNFAIP3 mutation are negative for Epstein-Barr virus. So, the 2 transformer events, involved in the pathogenesis of classical Hodgkin's Lymphoma, are mutually exclusive (2). Infection with HIV virus favours the emergence of Hodgkin's lymphoma, especially with mixed celularity or lymphocyte-depleted forms (it is 15 times more common in people infected with HIV than in the general population). Comparative genomic hybridization studies have determined that 4 gene correlates with an increased risk of classical Hodgkin's lymphoma disease: COX2, IL10, ILR4, IL18, a fact which underlines the importance of pathological cytokine signalization in the pathogenesis of the disease. Genetic variants of the genes involved in DNA repair are also associated with an increased risk of the disease (7). Study of microarray profiles of Hodgkin's lymphoma cell lines showed FOXC1 and FOXD1 gene overexpression and the lowering transcription of FOXP1, FOXO1, and FOXN3 genes , involved in the differentiation of B lymphocytes (8). Additionally, there is a silencing of apoptosis inducing genes BIK and INPP5D, an inhibitor of PI3K-related oncogenic pathway. There were identified 2 molecular subgroups of classical Hodgkin's lymphoma, depending on the intensity of the activity of the transcription factors of proto-oncogenes IRF4, MYC, and NOTCH1 (6). Increased exposure to ultraviolet radiation may have a protective role against the occurrence of Hodgkin's lymphoma, especially of those Epstein Barr virus positive. Among the plausible mechanisms involved would be: induction of ultraviolet radiation on the T regulatory lymphocytes or cellular response to DNA damage (9).

Evolution and prognosis: The European Organisation for Research and Treatment of Cancer (EORTC) established that patients with early stages Hodgkin's lymphoma which have one of the following risk factors have poor prognosis: ≥ 50 years old, bulky mediastinal lymph nodes, ESR ≥ 50 mm/1 h (or ≥ 30 mm/1 h if they have B symptoms), ≥ 4 regions involved. According to the German Hodgkin Study Group, the risk factors for patients with early stages disease are: bulky mediastinal lymph nodes, ESR ≥ 50 mm/1 h (or ≥ 30 mm/1 h if they have B symptoms), ≥ 3 regions involved and the presence of extranodal disease. If there are no risk factors, disease is considered in limited stage, and if there are 1 or more risk factors – in intermediate stage (10). EORTC also established and the risk factors for the disease in its advanced stages: age over 45 years, stage IV, male, albuminemia less than 40 g/l, hemoglobinemia under 10,05 g/dl, over 15,000 leukocytes/mm3 and under 600 lymphocytes /mm3 or below 8% (International Prognostic Score 0-7) (11). The study of gene expression profile, based on ARN signature from frozen lymph node sections of the patients that have not responded to the first applied treatment, found an increase in gene expression signature of macrophages, adipocytes, angiogenic cells, Reed Sternberg cell, with an overexpression of matrix metalopetidases and an underexpression of lymphocytes B genes of germinal centers. Immunohistochemistry confirmed that the presence of less than 5% macrophages (CD68+ cells) was correlated with a longer progression-free survival; in patients in early stages disease (IA and IIA) the absence of macrophages in lymph node sections was correlated with a disease-specific survival rate of 100%. CD68 is a superior prognostic marker comparing to IPS score on the prediction of disease free survival, according to several studies, including multivariate analysis. CD163 is another marker specific for monocytes/macrophages and it has similar meaning to CD68, but is more specific than this and allows identification of macrophages with more certainty (7). A large proportion of CD20+ cells dispersed on the background sections of classical Hodgkin's lymphoma lymph node seems to have a favourable prognosis regarding the progression-free survival and overall survival in this type of lymphoma, unlike the depletion of CD20+ cells on the background of histological preparations which coexist with an increased number of CD68+ tumor associated macrophages – a negative prognostic factor (12). The predictive value of PET-CT in examination after first course of polychemotherapy was studied in a group of 126 patients. It proved to have prognostic significance for progression-free survival and overall survival. Progression-free survival at 2 years for PET1-negative patients (made after the first chemotherapy cycle) was 98.3%, while for those PET1-positive – 40,8%. No other prognostic marker does identify a group of patients with a more favourable prognosis that the examination carried out after the first course of polychemotherapy (10).

Treatment

HL ESMO guide for 2014 recommandes for limited stage disease to make 2 ABVD cycles, followed by irradiation type ISRT with 20 Gy (10, 13). For the intermediate stages it recommandes 4 ABVD cycles, followed by radiotherapy type ISRT with 30 Gy; the young patients with good performance status can receive 2 escalated-dose BEACOPP cycles + 2 ABVD cycles, followed by irradiation type ISRT with 30 Gy. For advanced stages it is recommanded to make 6-8 ABVD cycles or 6 escalated BEACOPP cycles, followed by irradiation type ISRT with 20 Gy on PET-CT positives residual masses (and with dimensions greater than 2.5 cm after BEACOPP and greater than 2 cm after ABVD). The recommendations for patients with refractory or relapsed disease are: life-saving therapy (DHAP, ICE, IGEV) followed by high-dose chemotherapy and peripheral stem cell transplantation; brentuximab vedotin (BV) can be used in patients who releapse after high-dose chemotherapy and peripheral stem cell transplantation and in those noneligible for aggressive chemotherapy; some combinations which include gemcitabine can be used to increase the quality of life and to prolong the survival; allogeneic peripheral blood stem cells transplantation after reduced intensity conditioning can be taken into consideration at the young subjects, chemosensitive, to which the disease has relapsed after high-dose chemotherapy and peripheral stem cell transplantation (10, 13, 14). PET-CT prior chemotherapy allowed to increase the estimation of prechemotherapy tumor mass volume on average 8.8% and the postchemotherapy clinical target volume with 7.1% and contributed to a better delineation of radiotherapy on the affected lymph nodes, without a necessary increase of the dose of irradiation (INRT) (15). A tiral of phase 2 made on 22 patients with supradiafragmatic Hodgkin's lymphoma established that radiation therapy with breathing locked in deep inspiration was able to reduce the lung dose irradiation in average with 2Gy, and those of the heart with 1,4 Gy, without lowering the target doses applied for mediastinal lymphoma (16). Some patients have atypical and extranodale determinations of Hodgkin's lymphoma, which creates difficulties in choosing therapy, especially to diagnosis, in particular when there is liver or renal failure. A useful scheme for those with abnormal liver biochemistry is: cyclophosphamide, etoposid, prednisone, and procarbazine (17). BV product is a solution for very high risk patients, which improves the risk/benefit ratio with increased efficacy and low toxicity. Patients with progressive disease or releapse after autologus peripheral stem cells transplantation can receive life-saving chemotherapy, followed by therapy with BV, product containing an antimicrotubular agent (monomethyl auristatin E), which will be selectively deliver in CD30+ B-lymphocytes (from Hodgkin's lymphoma and CD30+ nonHodgkin's lymphoma) due to its coupling with anti-CD30 monoclonal antibodies (18) and which lead to cell cycle arrest in G2/M phase. An estimated overall response rate would be about 75% (19). Even if it is administered alone in patients with relapsed or refractory disease, it leads to an overall response rate of 75% and complete answers to 33% of them, a superior result of any tested agent or drug combination (19). The patients who relapsed after allogeneic peripheral stem cells transplantation can also be treated with BV (20). The addition of BV to reduced intensity conditioning scheme to patients with relapsed Hodgkin's lymphoma before the allogeneic peripheral stem cells transplantation has been a success, after a median follow-up 14.4 months. BV treatment before reduced intensity conditioning (fludarabine/melphalan) for allogeneic transplantation, allowed the reduction of the graft-related complications, of peritransplant toxicity and resulted in an increased progression-free survival at two years of 59.3% compared with 26.1% (without BV) and reduced the cumulative incidence of disease progression and releapses to 23.8% from 56.5% (21). For patients who have no transplant indication, there are ongoing studies that associate BV with chemotherapy (replacement of bleomicine, that has known toxicity, in ABVD or BEACOPP schemes) in limited forms of Hodgkin's lymphoma.

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