

Editorial

A Look at Today's Classical Hodgkin's Lymphoma

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The existence of Reed Sternberg cells in a reactive inflammatory environment defines the classic type of this malignant lymph proliferation. Its incidence is about 5/100,000 inhabitants/year, represents about 1% of cancer cases that occur annually [1], and is dependent of gender, age, geographic location, ethnic group and socioeconomic status. The highest rates of mortality due to its can be found in countries where the incidence of classic Hodgkin's lymphoma is the lowest and vice versa [2]. This type of 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 [3]. There is an interaction between the cells which populate the affected lymph nodes (Hodgkin's, Reed Sternberg, stromal, and reactive cells), involved in the pathogenesis of lymphoma. The origin of Hodgkin's and Reed Sternberg cells would be in the germinal centre cells (GC) or lymphocytes B post-GC, because the mutated gene coding the variable region of immunoglobulin was found in these cells [4]. Epstein-Barr virus can be implicated in the pathogenesis of classic Hodgkin's lymphoma by long-lasting antigenic stimulation and by saving the B cells from GC affected by apoptosis [3]. Another mechanism responsible for the proliferation of Hodgkin's and Reed Sternberg cells and which prevents their entrance into apoptosis is the activation of NF-kappaB. Epstein-Barr virus was not found in cells bearing the mutation of TNFAIP3 gene (which encodes a natural inhibitor of NF-kappaB). Concluding, these two transformer events (the presence of Epstein-Barr virus and the mutation of TNFAIP3 gene) are mutually exclusive [1, 5]. HIV virus favors the emergence of Hodgkin's lymphoma. Immunosuppression and poor viral control could be involved in

this process; especially during immune reconstitution in the period post combined antiretroviral treatment initiation [6]. The importance of pathological cytokine signalization in the pathogenesis of the disease is highlighted by comparative genomic hybridization studies which found that 4 genes (COX2, IL10, ILR4, and IL18) correlate with an increased risk of classical Hodgkin's lymphoma disease occurrence [7].

Study of comparative microarray profiling 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]. In addition, there is a silencing of apoptosis inducing genes BIK and INPP5D, an inhibitor of PI3K-related oncogenic pathway. There were defined 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 [4]. It seems that an increased exposure to ultraviolet radiation may have a protective role against the occurrence of Hodgkin's lymphoma, especially in patients positive for Epstein Barr virus. Between the plausible mechanisms, the following would be involved: induction of ultraviolet radiation on the T regulatory lymphocytes or cellular response to DNA damage [9].

Prognosis

The European Organization for Research and Treatment of Cancer (EORTC) established the risk factors predicting a poor prognosis in patients with early stages (if there are no risk factors, the disease is considered in limited stage, and if there are 1 or more risk factors – in intermediate stage) and advanced stages of Hodgkin's lymphoma [10]. The pres-

ence of each factor from IPS score for advanced Hodgkin's disease was found to reduce overall survival (OS) at 5 years by approximately 8%: patients with an IPS ≤ 1 had a 90+/-2% OS rate, which dropped to 59+/-2% among patients with IPS ≥ 5 [11]. Numerous CD20+ cells dispersed on the background sections of classical Hodgkin's lymphoma lymph node seems to have a favorable prognosis on progression-free survival and overall survival in this type of lymphoma, unlike the depletion of CD20+ cells on the same location which coexist with an increased number of CD68+ tumor associated macrophages – a negative prognostic factor [12]. CD163 is another marker specific for monocytes/macrophages, but is more specific than CD68 and help to the identification of macrophages with more certainty [7]. The presence of miR124a methylation advocates for an aggressive type of Hodgkin's lymphoma [13].

PET-CT could establish the prognosis of these patients. The predictive value of this examination realized after first course of poly chemotherapy 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%. The authors consider that no other prognostic marker does identify a group of patients with a more favorable prognosis that the PET-CT examination carried out after the first course of poly chemotherapy [10]. The presence of more than 0.0045×10^9 CD34+ myeloid-derived suppressor cells/l at the moment of diagnosis and/or PET-2 positivity predispose the patients to have a shorter progression-free survival, in accord with a recent study [14].

Treatment

The choice of treatment depends on the stage of disease. Estimation of prognosis and treatment response assessment by positron emission tomography scan can help to optimize them [15].

HL ESMO guidelines (2014) recommend for limited-stage disease 2 ABVD cycles and irradiation type involved site radiation (ISRT) with 20 Gy [10, 16]. The same guidelines proposes 4 ABVD cycles + 30 Gy ISRT (or 2 BEACOPPesc cycles + 2 ABVD cycles + 30 Gy ISRT for the younger patients with good performance status) if the disease is in intermediate stages. The patients with an advanced stage of disease could receive 6-8 ABVD cycles (or 6 BEACOPPesc cycles) + 30 Gy ISRT to residual lymph nodes which are PET-positive after the completion of chemotherapy. A recent meta-analysis of 11 trials which included 9993 patients established the efficacy of 6 BEACOPPesc cycles in these patients: the survival advantage over ABVD was 10% (95% CI, 3-15) after a median follow-up of 5.9 years; they had a 5-year OS rate of 95% [17]. For the relapse or refrac-

tory disease, HL ESMO guidelines recommend as standard of care the salvage chemotherapy + high-dose (HD) chemotherapy and peripheral stem cell transplantation. The patients who relapse after HD-chemotherapy and those who are not eligible for HD-chemotherapy have indication for brentuximab vedotin (BV). BV acts by blocking cell cycle in G2/M phase [18]. It has an acceptable profile of toxicity and can be safely combined with chemotherapy [19]. Even in mono therapy administered to the patients with refractory or relapsed disease, it was able to induce an overall response rate of 75% and complete answers to 34% of them [20]. The association between BV and bleomicine must be avoided due to the high risk of side effects, especially pulmonary toxic effects, seen after its administration as first-line therapy in naive treatment patients with advanced stage Hodgkin's lymphoma; the association of brentuximab vedotin plus AVD had no lung toxic effect at these patients [21]. BV used in patients unresponsive to upfront therapy or who relapsed after primary treatment allowed to reduce the tumor mass, in many patients reaching a PET negative status before autologous stem cell transplantation, and prolonging the outcomes after this therapeutic enhancement [22]. The treatment with BV before RIC-alloHCT was able to reduce the transplantation-specific comorbidity and peri-transplantation toxicities; the progression-free survival at 2 years was improved (59.3% versus 26.1%), and the incidence of relapse/progression was reduced (23.8% versus 56.5%) [23].

The combinations which include gemcitabine can prolong the life and contribute to the improvement of quality of life. The young patients who are chemo sensitive and relapse after HD-chemotherapy and peripheral stem cell transplantation can be treated with allogeneic peripheral blood stem cells transplantation after reduced intensity conditioning [10,16,24].

There are a lot of treatment related toxicities, including those involving the lung, the heart, the fertility, the hypothyroidism, and the second and the third neoplasias, the last due to the mutagenic effect of chemo- or radiotherapy. These can be: carcinoma, lymphoma, or non-Hodgkin's lymphomas [25]. The breast cancer is more frequent to females and pulmonary cancer to men. But in the past few years, the x-ray field size was reduced (from mantle field and involved field radiation to involved node and even involved site radiation) and the doses, too (to 20-30 Gy), so that it is to be expected that the frequency and the severity of side effects will diminish. According to a recently published study, surrender of radiotherapy does not seem to be an acceptable solution. The omission of radiotherapy to a large number of patients in 2003-2010 era comparing to 1995-2002 period conducted to a survival reduction at 5 years of 93.3% versus 95.1% ($P=0.013$), without any reduction in risk of second malignancies [26]. The lung dose irradiation could be reduced in average with 2Gy, and those of the heart

with 1,4 Gy when the radiotherapy was made with breathing locked in deep inspiration, without any lowering of the target doses for mediastinal lymphoma [27]. Proton therapy could be another solution to reduce the treatment-related toxicity due to the fact that this treatment modality has the potential to deposit a high dose only at the target [28] but it requires additional studies.

A less liver toxicity can be obtained using a scheme which includes cyclophosphamide, etoposide, prednisone, and procarbazine, especially for the patients with abnormal liver biochemistry [29].

If autologous peripheral stem cell transplantation proved to be useful for prolonging survival in patients with relapsed and refractory HL (overall survival at 3 years was 70% in a Japanese study), the role of allogeneic peripheral stem cell transplantation is yet not established (in the same study overall survival at 3 years was only 45%) [30]. A solution for non-responders or refractory patients could be the inclusion in clinical trials.

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