Onset Risk Factors and Treatment Response Features of Refractory Hodgkin Lymphoma

Oana STANCAa; Anca Mariana CIOBANUb; Anca Roxana LUPUc; Cecilia GHIMICIb; Irina TRIANTAFYLLODISa; Andrei COLITAb; Ileana Delia MUTb

a“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
bDepartment of Hematology, Coltea Clinical Hospital, Bucharest, Romania

ABSTRACT

Background: The International Prognostic Factors Project on Advanced Hodgkin lymphoma (HL) developed a seven factor prognostic score consisting of gender, age, stage, serum albumin, hemoglobin, leukocytosis and lymphocytopenia for the newly diagnosed Hodgkin disease patients in advanced stages, who receive chemotherapy.

Objectives: The purpose of this study was to determine whether this prognostic score would also be useful for refractory Hodgkin lymphoma patients in monitoring response to treatment.

Material and method: In the period 2000-2012, we performed a study on a group of 91 patients to show that the prognostic factors identified by the International Prognostic Factors (IPF) score affect the event-free survival (EFS) and the overall survival (OS). Our study also intends to show that the results of these factors change with the treatment response in patients with HL included in the category of patients with refractory disease.

Results: B symptoms, onset lymph node, more than 3 areas involved, bulky disease, extranodal involvement, low serum albumin, erythrocytes sedimentation rate (ESR), C reactive protein (CRP), lactic dehydrogenase (LDH) and anemia were associated with poorer EFS and OS. Male gender, stage, histological type, age (>45 years) and leukocytosis were not associated with significantly poorer outcomes.

Conclusions: the prognostic score for advanced disease is also useful in predicting relapse in patients with HL and early detection of response in patients with refractory HL.

Keywords: Hodgkin lymphoma (HL), prognostic factors, response to treatment

OBJECTIVES

The multivariate statistical analysis of many different groups of patients in specialized centers has led to the identification of prognostic factors included in the IPF index on advanced Hodgkin disease. This score comprises seven factors (serum albumin <4g/dl, hemoglobin <10.5 g/dl, male gender, age >45 years, Ann Arbor stage IV disease, white blood cell count >15.000/mm³, and lymphocyte count <600/mm³ and /or <8% of the total white blood cell count) (1-6). Each of these factors was independently associated with a similar risk of disease progression following primary
The study was conducted on a sample of 91 patients admitted in Coltea Hospital during 2000-2012. These patients were diagnosed with Hodgkin lymphoma after histopathological examination and immunohistochemistry. Selected patients had at least 4 cycles of chemotherapy: ABVD (Adriablastin, Bleomycin, Vinblastine, Dacarbazine), BEACOPP (Bleomycin, Etoposide, Adriablastin, Cyclophosphamide, Vincristine, Procarbazine, Prednisolone) and other polychemotherapy courses and/or radiotherapy.

**Patient characteristics:**

- In terms of distribution of patients with HL, from the total number of patients enrolled, 37 had refractory disease.
- In the general study group, 48% were women and 52% men. Out of the patients with refractory disease, 57% were women and 43% men. Although, according to literature, male is a negative prognostic factor, females represented a higher percentage of progressive disease in our group of patients.
- Regarding the histological subtype distribution of HL, the nodular sclerosis (NS) was the most frequent subtype in the overall patient group.
- In the general study group of patients, the polychemotherapy treatment frequently used was ABVD, followed by BEACOPP treatment.
- The same frequency of use of the ABVD cure type was observed in patients with refractory disease.
- Most of the patients in the general study group were not treated with radiotherapy, a similar proportion being found in patients with refractory disease.
- A small number of patients have received stem cells autotransplantation.

The variables assessed at diagnosis, analyzed as potential prognostic factors, were: age, sex, histological subtype, Ann Arbor staging, presence or absence of B symptoms, extranodal onset, the presence or absence of lung, liver, bone marrow disease involved, hemoglobin level, serum albumin, ESR, LDH, CRP lymphocyte count number in absolute or relative value and sideremia.

Out of the prognostic factors enumerated (Table 1) for our group of patients with refractory Hodgkin lymphoma, the following factors...
with statistical significance emerged: onset lymph node involvement of more than 3 nodal areas, serum iron, B symptoms, low serum albumin, ESR, CRP, LDH.

**RESULTS**

- Regarding the relationship of sideremia with refractory disease, the serum iron levels correlate with refractory disease to a power p=0.08, a test to the limit of statistical significance.
- Patients with progressive disease HL had hemoglobin values ranging from 8.5 to 10.5 g / dl (Figure 1).
- From the group of patients with refractory HL, 12 patients had more than 3 nodal areas involved at onset.
- Survival without disease events in patients with B symptoms and ESR <30 mm/h, was higher compared to those with ESR ≥30 mm/h: 40.1 months versus 21.4 months (p = 0.02) (Figure 2).
- The high level of ESR was correlated with failure to response to treatment.
- The subgroup analysis revealed a statistically significant association (p = 0.002) between the ESR and relapse (Figure 3).
- The C-reactive protein level was higher in the group of patients with relapse [6.4 [-0.7 to 13.6] mg/dL versus. 2.1 [0.9 to 3.4] mg / dl, (p = 0.02) than in the group of patients with progressive disease (p = 0.006) (Figure 4)
- Patients who did not respond to treatment had the highest serum LDH levels compared to those who responded to treatment (p = 0.05).
- The difference in overall survival between patients with refractory disease and those without disease refractory (p = 0.02) (Figure 5).

**CONCLUSIONS**

According to literature, although it is considered a highly curable malignancy hemopathy, about 1/3 of the patients with Hodgkin lymphoma were found to be unresponsive or relapsed after initial therapy (5,7,8). The high-dose chemotherapy followed by autologous stem cell transplantation is the standard treatment for patients who relapsed after or were refractory to initial therapy (5-7). The stem cell allotransplant is indicated in cases which are refractory to chemotherapy or after the failure of the autotransplant (7).
The Hodgkin lymphoma, however rare globally, tends to have an incidence on the increase.

The modern techniques to identify the Reed Sternberg cell and its mononuclear variant, the Hodgkin cell- whose origin is still controversial- allow for an increased diagnosis of the disease.

New therapeutic agents and biological targeted therapies are now available but the challenge still remains to maintain a high rate of cure with low toxicity and long-term treatment-related characteristics and identification of markers for inclusion of refractory cases within appropriate regimens.

A comprehensive approach with all clinical and biological factors with a potential impact on patient prognosis and individualized treatment can be a good guide for choosing the most effective therapies.

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REFERENCES


