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Hematological delineation of primary non-Hodgkin's lymphomas of the spleen: diagnostic and prognostic significance

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Objective: The purpose of this multicentric study was to determine the specific hematological features of primary splenic stage IV non-Hodgkin's lymphomas (NHL), that could be used as the diagnostic criteria and prognostic factors.

Materials and Methods: Hematological findings were analyzed in 145 patients with primary splenic stage IV NHL (age range 15 - 82 years). According to the N.C.I. Working Formulation and World Health Organization Classification, low-grade (LG) histological types were identified in 107 (75.4%) cases, and high-grade (HG) histological types - in 38 (24.6%).

Results: Bone marrow involvement was revealed in 106 (99.1%) cases of LG NHL, occurring less frequently in HG NHL (20 cases/52.6%). The hematological abnormalities were registered at the stage of bone marrow involvement. Leukemic phase was detected in 89 (83.9%) and 6 (30.0%) patients, respectively. In cases without leukemic phase cytopenias were common. In LG NHL, anemia and thrombocytopenia were found in 13 (76.5%) patients, leukopenia in 12 (66.7%). In HG NHL, these cytopenias developed in 13 (92.9%), 6 (42.9%), and 8 (57.1%) cases, correspondingly. Patients with leukemic phase presented anemia, leukopenia, leukocytosis, and thrombocytopenia with following frequency: 75/84.3%, 20/22.3%, 37/76.5%, and 46/51.7% in LG NHL; 4, none, 2, and 4 of 6 in HG NHL. In LG NHL without leukemic phase the median lymphocyte count constituted 26.5 ± 1.7%, in those with leukemic phase - 70.9 ± 4.2%. In the bone marrow aspirates, the median lymphocyte count was 25.2 ± 2.11% and 51.4 ± 2.78%, respectively. In HG NHL, the median blast cell count in the bone marrow was 7.1 ± 0.91% in cases without leukemic phase, and 33.3 ± 5.97 in those with leukemic phase. Cytopenias, lymphoid cell count in the peripheral blood and in the bone marrow didn't correlate with the spleen size. In LG NHL, median lymphocyte count in the peripheral blood was superior to that registered in the bone marrow, and the nodular bone marrow involvement in the form of follicular structures was predominant (56.0%). In HG NHL, the disseminated microfocal lymphomatous bone marrow infiltration with blast cells was common (78.6%). In LG NHL, the 5-year survival was 70.0% in cases without leukemic phase, being higher ($P < 0.05$) than in cases with leukemic phase (53.0%). In HG NHL, the median longevity was 23.5 and 4.7 months, respectively ($P < 0.01$).

Conclusions: The realized researches pointed out the characteristic hematological aspects of primary splenic stage IV NHL, that might serve as an important diagnostic criteria. In all the histological types of primary NHL of the spleen leukemic phase was determined as a poor prognostic factor.

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Evaluation of cyclic chemotherapy in non Hodgkin's lymphoma patients infected with chronic hepatitis.

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Aim: To evaluate the safety of administering cyclic chemotherapy in patients with Non Hodgkin's Lymphoma and chronic hepatitis.

Patients and methods: An evaluation of patients treated for Non Hodgkin's Lymphoma between 1996 and 2002 was carried out. Patients infected with chronic hepatits B or C were identified. A total of 29 patients had chronic hepatitis B or C in association with Non Hodgkin's Lymphoma. Out of 29 patients fifteen were hepatitis C positive and fourteen were hepatitis B positive. The characteristics of patients were as follows: median age 49 years (range 20-84 years) with 22 males and 7 females. There were six patients each with stage I, II, III disease and eleven patients with stage IV disease. Three patients had liver involvement due to lymphoma. Pathologic subtypes were Follicular variety in 8 patients, Diffuse large cell and its subtypes in 20 patients and Burkitt's like in 1 patient. IPI was low risk in fourteen patients, low intermediate in six patients,high intermediate in seven patients and high risk in two patients. At baseline Pugh-Child's score for grading of severity of liver disease was score A in 19 patients, score B in 7 patients and score C in 3 patients. Twenty four patients received anthracycline based chemotherapy while three patients received oral alkylating agents. Two patients did not receive any chemotherapy. Patients were followed with liver function tests done at baseline, during treatment, and three months after completion of chemotherapy.

Results: The median number of chemotherapy cycles administered was 6 cycles (range 1-8 cycles). Mean baseline values were bilirubin 10.2 micromol/l, ALT 47 IU/l, AST 41 IU/l and albumin 35 g/l. Mean values during treatment were bilirubin 12 micromol/l, ALT 53 IU/l, AST 43IU/l and albumin 33 g/l. Mean values 3 months after completion of chemotherapy were bilirubin 9 micromol/l, ALT 59 IU/l, AST 43 IU/l and albumin 35 g/l. One patient required treatment interruption due to abnormal liver function tests and developed progressive liver failure. This patient had early cirrhosis and Pugh-Child's score C at baseline. One patient died during chemotherapy. The cause of death was unrelated to hepatitis. Values for viral load were not available in all patients so they are not reported here.

Conclusion: Chemotherapy can be safely administered to patients with chronic hepatitis B or C. Based on our observation no dose modification is required in patients with normal liver function tests and absence of cirrhosis at baseline. Patients should be closely monitored with regular liver function tests during the chemotherapy.

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Late toxicity of radiotherapy (RT) and chemotherapy (CT) for malignant lymphomas

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Purpose: To assess the degree of late complications of radiotherapy (RT) and chemotherapy (CT) in patients succesfully treated for malignant lymphomas.

Patients and Methods: Long-term side effects were evaluated in 142 patients who were in a complete remission for 3 years or more after having received 35-45 Gy and/or minimum 3 courses of CT (101 patients). The following investigations were performed: clinical examination, pulmonary function tests, chest X-ray, cardiological investigations including echocardiography, haematological investigations, bone marrow cytology and thyroid function tests.

Results: Reduced performance status and deteriorated general condition was found in 48%, mediastinal or paramediastinal fibrosis in 72% (severe in 7% and moderate in 39%), slight (20%) and moderate (8%) fibrosis of the apical parts of the lung, ventilation disorder in 64%, mostly of restrictive type, ventricular ventilation disorder in 18%, cardiac insuficiency in 11%, pericarditis in 7%, granulocytopenia in 11%, lymphocytopenia in 33%, slight anemia in 24%, aplasia in 60% and hypoplasia in 27% on sternal marrow cytology (previously irradiated) and hypoplasia in 16% on the iliac crest cytology (not irradiated), clinically manifested hypothyroidism in 2 patients, elevated TSH in 27%. 13% of investigated patients received supported therapy.

Conclusion: The fact that more than 50% of patients showed pathological findings signals the need for further detection of late complications of RT and CT and the need for administration of additional supportive therapy.

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Study on prognostic factors and on role of radiotherapy (RT) in patients (pts) with aggressive Non Hodgkin's Lymphomas (NHL) treated with MACOP-B or VACOP-B chemotherapy (CT)

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Background: In advanced high grade NHL chemotherapy is basic treatment modality and the role of RT has not been clearly defined.

Material and methods: A retrospective analysis of treatment results was performed in the group of 120 pts with advanced high grade NHL treated initially with MACOP-B (24 pts) or VACOP-B (96 pts). There were 84 male and 36 female, median age was 52 years (18-72), 95 pts had stage III or IV disease. Radiotherapy (RT) was given to 37 (31%) of patients. Indications to RT included: initial bulky disease of lack of CR after CT. Median dose of 36 Gy in 20 fractions was delivered. End points of the study have been 5 year relapse-free survival (5-y RFS) and overall survival (OS). Kaplan-Maier method and log rang test were used for survival analysis. Multivariate analysis of clinical and therapeutic prognostic factors was performed with Cox's model.

Results: With median follow-up time 32 months 5 year OS and RFS were 46% and 38,5% respectively. After CT CR was obtained in 77 pts, PR in 35, PD in 8 pts (4 of whom died during treatment). Following RT the rates of CT and PR was 70% (84 pts) and 23% (28 pts) respectively. Univariate and multivariate analysis shoved that: stage, extranodal involvement, performance status, LDH level, international prognostic index have

been significant prognostic factors for survival. 5-y RFS in pts who received RT was 51% and in pts treated with CT alone was 32% (p=0,0767). RT appeared to improve survival in pts who did not received full CT course, without CR and in pts with low and intermediate IPI risk categories.

Conclusions: In pts with advanced high grade NHL we obtained 45,7% 5yOS and 38,4% 5-y RFS. In patients irradiated post CT 5-y RFS was 51%. RT improves survival in selected pts categories.

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Evolution of lymphocytopenia prognostic value in advanced Hodgkin's disease: a single-center experience.

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Background: Lymphocytopenia (lymphocyte count <600/mm^3 or <8% of WBC, or both) is one of seven factors combined into a prognostic score according to International Prognostic Factors Project. In attempt to separate a distinct group of patients with advanced Hodgkin's disease (HD) at very high risk of early progression, we retrospectively evaluated 1070 patients with stage III-IY and/or bulky and/or B-symptoms HD, referred to our Department between 1976 and 2000.

Methods: In order to analyze the incidence and significance of lymphocytopenia (LP) for clinical outcome the patients were divided into three subgroups according to one of three LP criteria: decrease of both absolute and relative counts (gr. 1, 32 patients); only relative LP (gr. 2, 43 patients); only absolute LP (gr. 3, 28 patients). All patients were treated with at least six courses of chemotherapy (COPP alone until 1988 in 597 patients; alternating or hybrid COPP/ABVD since 1989 in 474 patients) with or without radiotherapy. Clinical outcome in terms of freedom from progression (FFP) and overall survival (OS) were compared between the three groups. All patients were followed until death or at least for two years.

Results: The distribution of LP incidences was similar within the two historical series; the three groups accounted for 3%, 5% and 2% of total study population, respectively. There were at least 50% overlaps with other prognostic factors in each group, forming characteristic clusters: in gr. 1 - Hb < 10.5 g/dl was found in 50-70% of cases; in gr. 2 60-80% of patients were males with WBC > 15.0/mm^3; gr. 3 was presented by patients of age > 45 years (43%), males (43%), with Hb < 10.5 g/dl (50%). Still the treatment outcome during first decade was similar in all three groups (FFP at 2 years was 30%, 5 year OS was 50%) and during second decade the outcome in gr. 1 did not improved. Meantime the outcome in patients of gr. 2 and gr. 3 was clearly improved during the second decade (FFP at 2 years 78% vs 36% and 100% vs 33%, respectively; 5 year OS 83% vs 51% and 100% vs. 50%, respectively).

Conclusions: Combination of absolute and relative lymphocytopenia appears to be strong factor of adverse prognosis deserving further attention.

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The role of hepatitis C virus (HCV) treatment in HCV-related B-cell non-Hodgkin's lymphoma (NHL)

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We have previously shown an epidemiological link between HCV infection and B-cell NHL in our geographical area. Indeed, some biological observations so far may indirectly suggest a link between virus and lymphomagenesis, such as the ability of lymphomatous cells to bind viral E2 envelope protein. Furthermore, recently, antiviral therapy against HCV revealed to be efficacious also against HCV-related splenic lymphoma with villous lymphocytes. In January 2001 we planned to test the effect of anti-HCV therapy on indolent low grade B-cell lymphoma (according to REAL classification) both at diagnosis and at relapse. Patients were requested to have well measurable nodal or extranodal disease, during the study no chemotherapy was allowed. Treatment consisted of pegilated alpha-interferon 50 microgram once a week and daily ribavirin 1 gr a day. Up to now, among the 5 patients entered the study. Three patients are evaluable. The first patient was enrolled in January 2001 while showing marginal zone nodal lymphoma that interested preauricolar and mammary lymph nodes together with bone morrow localization (40%). She was born in 1959. Since 5 years before she was affected by chronic viral C hepatitis with minimal activity (bioptic diagnosis), genotype 2a/2c. She began the treatment while showing an HCV viral load of 17820000 Eq/ml. During treatment lymph nodes disappeared and after 6 months bone marrow localization showed a decrease of 50% (good partial response), at the same time viral load disappeared. The second patient, enrolled in August 2001, showed a nodal relapse after one and half year of a previous marginal zone mucosa associated lymphoma of the palatum. The relapse concerned numerous retroperitoneal nodes with a maximum diameter of 2,5 cm and bone marrow. The patient was affected by chronic active viral C hepatitis from 1993 with about a 3-time increase of transaminases. After 6 month of treatment viral load was decreased of about 3 logs, marrow involvement disappeared such as retroperitoneal involvement (complete remission). The patient experienced grade III toxicity for platelet and white blood cells, which improved with reduction of dosage. The third patient partially evaluable is a woman 72 years old, affected by chronic viral C hepatitis (genotype 2a; ALT and AST in normal range) that showed in December 2002 the third relapse of follicular cutaneous lymphoma so she also underwent PEG-Intron and ribavirin. Now is under treatment with a decrease of cutaneous lesions. This experience proves that efficacious antiviral treatment in HCV related indolent lymphoma might modify the course of the lymphoma.

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Dexamethasone, etoposide, ifosfamide, and cisplatin (DVIP) as salvage therapy in low- grade Non Hodgkin's lymphoma (NHL), following prior anthracycline containing therapy

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Introduction: The combination of dexamethasone, etoposide, ifosfamide, and cisplatin (DVIP) was shown to be active in histologically aggressive NHL following prior therapy that included doxurubicin (Haim et al. Cancer 80:1989, 1997). We, therefore, evaluated DVIP as a salvage chemotherapy following prior anthracycline containing therapy in patients with low- grade NHL.

Patients and Methods: Original DVIP consisted of dexamethasone 20mg x 2, days 1-4, etoposide 75mg/m2, days 1-4, ifosfamide 1200mg/m2, days 1-4, and cisplatin 20mg/m2, days 1-4. All drugs were given IV,and cyles were repeated every 3 weeks. Initial drug doses were reduced according to standard criteria and ranged between 10%-100%, median 60%. Between May 1990 and June 2002, 44 patients (23 males and 21 females, age: 29-84, median age 61 years), with histologically confirmed low- grade NHL were treated with DVIP at our center.The most common histological subtype was follicular small cleaved (Working Formulation), (20 patients, 45%) . Prior therapy included two or more combinations in 32 patients (73%), WHO performance status was grade 2 or more in 27 patients (61%), serum LDH was elevated in 18 patients (41%). Eighteen (41%) had B symptoms and 8 patients (18%) had bulky disease.

Results: All patients were evaluable for toxicity, and 42 were evaluable for response. Partial response (PR) was achieved in 14 patients (33%) ,and complete response (CR) in 13 patients (31%) (overall response rate 64%). Complete response rate was higher among patients who had achieved CR with prior therapy compared to those who had not achieved CR (11/26, 42% vs. 2/18, 11%). Median survival time was 12 months for the entire group and 114 months for complete responders.

The main toxicity of DVIP was myelosuppresion. Grade 4 leukopenia was noted in 9 patients (20%), grade 4 thrombocytopenia was in 3 patients (7%), and grade 4 anemia was in 3 patients (7%). Neutropenic fever that required IV antibiotics developed in 8 patients (18%) and in 8/186 cycles (4%) .Red blood cell transfusion was required in 7 patients (16%) in 11 cycles (6%). Due to myellosuppression further dose reductions were required in most patients. Non- hematological toxicity was moderate. There were no drug related deaths.

Conclusions: DVIP is active regimen in low-grade NHL following prior anthracycline-containing chemotherapy, and might induce durable remissions.

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Analyses of percentage CD23 cell membrane molecule expressed in ratio to the immunoglobulines concentration in B-CLL.

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Background: B-CLL is a malignancy characterized by accumulation of terminally differentiated B cells. However, with increasing number of peripheral lymphocyte number (PBL) and advance stage of disease, usually