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The results of treatment in patients with non-Hodgkin's lymphoma (NHL). The analysis of prognostic factors and evaluation of the role of radiotherapy (RT)

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Purpose: The estimation of the results of treatment and evaluation of the role of RT in patients with NHL.

Methods: Between 1986–95 120 patients (36 women and 84 men) with intermediate (76 pts.) or high (44 pts.) grade NHL were treated in the Centre of Oncology in Kraków. There were 7 pts. in stage I, 18 pts. in stage II, 41 pts. in stage III, and 54 pts. in stage IV (Ann Arbour classification). "B" symptoms were observed in 38 patients (33%), and in 33 pts. bulky disease was found. The International Prognostic Index (IPI) was defined in 103 patients: 8 pts. were in low, 34 pts. - in low/intermediate, 32 pts. - in high/intermediate, and 29 pts. - in high risk group. All patients were treated with chemotherapy (CT) with MACOP-B (24 pts.) or VACOP-B (96 pts.) regimens. RT was applied in 37 pts. An indication for RT included: initially bulky disease, partial response (15 pts.) after CT and extranodal localisation. The median dose of RT was 36 Gy.

Results: The 5-year overall survival rate for whole group was 45.7%, and 5 year relapse-free survival rate was 38.4%. The univariate analysis confirmed prognostic significance of: performance status, III and IV stage of diseas, extranodal localisation, high level of lactate dehydrogenase, IPI, anemia. In multivariate analysis the significant prognostic factors for overall survival were: III and IV stage of disease, high level of lactate dehydrogenase, and for relapse-free survival: extranodal localisation, high level of alpha-2-globulin, which was positive prognostic factor.

The higher relapse-free survival was observed in group of patients who received combined treatment (CT + RT): 51% vs. 32.4%. The favourable effect of RT on treatment results was observed especially in patients: with bulky disease, III or IV stage of disease, high risk group (IPI), in pts. with only partial response after CT.

Conclusions: Results indicate that RT after CT may improve relapse-free survival in high risk patients with intermediate or high grade NHL.

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Six-week rituximab monoclonal antibody therapy for chemotherapy-pretreated advanced low-grade non-Hodgkin's lymphoma: Efficacy and toxicity of a phase II study

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Purpose: Previous clinical trials demonstrated, that four or eight weekly infusions of Rituximab in patients with relapsed or refractory low-grade non-Hodgkin's-lymphomas (NHL) were well tolerated and had significant clinical activity with overall response rates of 40–60%. We investigated the efficacy and toxicity of six weekly doses of Rituximab in prolonged chemotherapeutically pretreated relapsed or refractory low-grade NHL-patients.

Methods: After pretreatment (median duration 33 months) with different cytostatic drugs (median 2, range 1–18) 66 patients with low-grade NHL (histologic subtypes: CLL n = 12, immunocytic n = 30, follicular n = 21, mantle cell n = 1, others n = 2) received six weekly doses of 375 mg/m^2 of Rituximab.

Results: All patients are evaluable for toxicity, 48 patients for response. The overall response rate was 37% (12/48 CR, 25%, 17/48 PR, 35%) with a median progression free survival of 16 months. WHO-grade I (0–9%) or II (0–4%) adverse events were the majority of reported toxicities and occurred most frequently with the first infusion.

Conclusions: The efficacy and safety profile achieved in this phase II study of six weekly doses of Rituximab compares favorably with those seen with four or eight weekly infusions in pretreated low-grade NHL. Rituximab represents an important a gent for a specific, low toxic treatment of B-cell-NHL and looks very attractive to be incorporated in primary and/or secondary chemotherapy protocols.

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Phase II study of palliative low-dose local radiotherapy in disseminated indolent non-hodgkin's lymphoma (INHL) and chronic lymphocytic leukaemia (cll)

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Introduction: INHL and CLL are highly sensitive to radiotherapy. Previous retrospective studies had shown high response rates of local palliative radiotherapy of 4 Gy in 2 fractions, which prompted this prospective phase II trial of the palliative effect of this regimen in patients with disseminated INHL or CLL.

Methods: 22 patients (11 males, 11 females, median age 62 years, range 30-89 years) with disseminated INHL (15 pts.) or CLL (7 pts.) were treated with the aim of achieving palliation from localised lymphoma masses with local low-dose radiotherapy, 2 Gy x 2 over 3 days. The patients were treated to a total 31 different sites. 17 of the patients had previously been treated with chemotherapy. The median observation time after start of radiotherapy was 8 months (range 3-26 months).

Results: All patients and all irradiated sites were evaluable for response. 18 of the 22 patients responded to the treatment, corresponding to an overall response rate (RR) of 82%, 12 patients (55%) achieved a complete remission (CR), 5 patients (22%) a partial remission (PR), and one patient had a CR at 3 sites and a PR at 1 site. 27 of the 31 irradiated sites responded to treatment corresponding to an overal RR of 87%, in 20 sites (65%) a CR was achieved, in 7 sites (22%) a PR. Patients with disseminated INHL had an overall RR og 87% (74% CR, 13% PR); patients with CLL had an overall RR of 71% (29% CR, 42% PR). The median duration of response has not yet been reached. The estimated percentage of responding sites still in remission after one year is 90%. None of the patients had any side effects of the treatment.

Conclusion: Low-dose irradiation (4 Gy in 2 fractions) is a highly effective palliative treatment of localised lymphoma masses in patients with disseminated INHL and CLL. The treatment has minimal side effects.

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Radiation therapy results for primary orbital non-Hodgkin's lymphoma

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Purpose: This study is to report local control rate, pattern of failure, and ocular morbidity after radiation therapy (RT) for primary orbital non-Hodgkin's lymphoma (PONHL).

Methods: Retrospective analyses were done on 34 orbits (in 29 patients) with PONHL who were given definitive local RT from March 1995 to August 1999 at Samsung Medical Center. All patients received RT with either single anterior field or paired wedge fields using 6~20 MeV electrons or 4~6 MV photons. In 26 cases, the lens was shielded either by custom-made block or shielding contact lens, while the entire lens was included within the radiation volume in 8 cases. The fractionation schedule was to give five daily treatments per week and the fractional radiation dose was either 1.8 or 2 Gy. The median total radiation dose to the lesion was 36 Gy (range: 26~45 Gy).

Results: There were 13 males and 16 females, and the median age was 40 years (range: 25~87 years). Five of 29 patients had bilateral involvement and thus total 34 orbits were treated. The primary sites of involvement were the retrobulbar area in 13 cases (38.2%), the conjunctiva in 10 (29.4%), the eyelid in 8 (23.5%), and the lacrimal gland in 3 (8.8%). Pathologic types were low grade marginal zone B cell lymphoma in 31 cases (91.2%) and mantle cell lymphoma in 3 (8.8%). After the median follow-up of 45 months (range: 16~74 months), no local recurrence and two distant relapses were observed. One relapse in the stomach found at 28 months of RT was managed with subtotal gastrectomy, and the other in the contralateral facial subcutaneous tissue found at 29 months was managed with local RT. Acute side effects by RT including skin change and keratitis were minimal. Symptomatic late reactions included cataract (3 cases) occurring among 8 cases where lens shielding was impossible, and retinopathy (3 cases)

occurring among 8 cases who were treated with electron energy of 12 MeV or higher.

Conclusions: Local RT for PONHL is very effective in achieving local control, and close long-term follow-up is warranted considering late distant relapse and morbidity. Lens shielding and use of electron energy lower than 12 MeV are important technical factors to be kept in mind to decrease late morbidity risk.

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Antileukemic and cytogenetic effects of two chemotherapeutic schemes CHOP and AHOP (A= aza-steroidal alkylating ester)

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Purpose: CHOP is one of the most well established and widely used chemotherapeutic schemes against lymphomas. Although CHOP has been proved highly effective, its genotoxic activity produces a high percentage of secondary tumors. Our previous studies on the antileukemic activity of an homo-aza-steroidal alkylating ester (ASE), showed good results, lower genotoxicity than cyclophosphamide and synergism with anthracycline activity. In this study we adjusted CHOP on mice for the treatment of P388 and L1210 leukemias and comparatively we adopted ASE in CHOP in replacement of cyclophosphamide, creating a new experimental treatment scheme (AHOP).

Methods: BDF1 mice were used for the evaluation of the antileukemic activity. Experiments were initiated on day 0 by implanting i.p. of 10^5 and 10^6 ascites cells of lymphoid L1210 and lymphocytic P388 leukemias. Administration was begun either on day 1 as a single injection of CHOP(C= 112, H=7.5, O= 0.21, P= 15 mg/kg) and AHOP (A= 13, H= 7.5, O= 0.21, P= 15 mg/kg) or on day 5 for P388. The antitumor activity was assessed from the oncostatic parameter T/C%. For the cytogenetic experiments 1 h before i.p. injection of 5-bromodeoxyuridine adsorbed to activated charcoal P388 tumor bearing mice treated i.p. with either CHOP or AHOP, at 1/10 of the dose giving for the surviving testing, were investigated for sister chromatid exchange (SCE) rates and proliferation rate indices (PRI).

Results: Three groups of P388 and L1210 leukemias were treated with CHOP and AHOP. Both treatment schemes were highly effective, causing 100% cures (6/6), when leukemias P388 and L1210 were treated on day 1 post transplantation. They, also, showed significant antileukemic effect producing T/C values of 308 and 257% for CHOP and AHOP, respectively, when advanced P388 leukemia on day 5 was treated. Both schemes produced significant increases in SCE-s however AHOP induced higher SCE frequencies and lower PRI levels than CHOP in P388 leukemic cells in vivo.

Conclusion: Both treatment schemes were determined to be extremely effective and the therapeutic activity depends on the treatment schedule (day 1, day 5) where CHOP was slightly more effective than AHOP in advanced P388 leukemia. However, the most effective scheme in inducing cytogenetic effect was CHOP. This study is in progress and these preliminary results should be investigated furthermore as a potential antitumor scheme.

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Incidence of anemia in CHOP-treated intermediate-Grade Non-Hodgkin's Lymphoma (IGNHL)

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Purpose: To evaluate the CHOP therapy-induced anemia rates and associated factors in IGNHL.

Methods: A practice pattern study was conducted at twelve community and academic oncology sites. Data on 591 IGNHL patients treated with CHOP chemotherapy were retrospectively collected. Data on patients with available baseline chemotherapy hemoglobin (Hb) value were analyzed (546 patients).

Results: The overall mean drop in Hb from baseline to the lowest value measured during chemotherapy was 2.3 g/dl (95% confidence interval, 2.18, 2.46). Of the 353 patients who had a normal Hb (> 12.0) at baseline, 28.3% (100 patients) developed moderate to severe anemia (< 10 g/dL) during chemotherapy and patients 60 years and older had a significantly higher risk (odds ratio 2.5) of developing anemia. Examining the persistence of anemia throughout all chemotherapy cycles shows that of the 62/546 patients with baseline Hb <10 g/dl, 47.5% of the patients failed to recover to a ≥ 10 level during chemotherapy. Anemia treatment data were not available. Similarly, 131/546 patients whose baseline Hb was between 10-12 g/dl dropped below the Hb level of 10. In addition, anemia and neutropenia were found to be significantly associated. Among patients who developed anemia, there was a higher incidence of patients with febrile-neutropenia (FN). FN was documented in patient charts by their treating physician. The following table summarizes the distribution of patients with anemia (chemotherapy-induced) and documented FN.

NCI Anemia Scale	Hb (g/dL)	Total N (%)	Documented FN n (% of N)
Grade 0 (WNL)	> 12.0	95 (17.4)	7 (7.4)
Grade 1 (mild)	10 - 11.9	209 (38.3)	43 (20.6)
Grade 2 (moderate)	8 -9.9	181 (33.2)	74 (40.9)
Grade 3 & 4 (serious to life-threatening)	< 8.0	61 (11.2)	32 (52.5)

NCI Anemia Scale: National Cancer Institute anemia grading scale. WNL: Within normal limits. N: No. of patients in each anemia grade. n: No. of patients in each grade anemia grade with documented FN

Conclusion: Treatment of IGNHL patients with CHOP chemotherapy results in anemia. Also, there is an association between CHOP induced anemia and FN.

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Modified ESHAP as salvage chemotherapy for recurrent or refractory non-Hodgkin's lymphoma: experience at Hacettepe university and a review of the literature

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We have evaluated the clinical efficacy and toxicity of a modified etoposide, methylprednisolone, cytarabine and cisplatin (ESHAP) chemotherapy regimen that has been used by the Hacettepe University Department of Medical Oncology (Ankara, Turkey) since 1993. Thirty-two patients (18 men and 14 women) with refractory or recurrent non-Hodgkin's lymphoma (NHL) were enrolled in this study. The median age of patients were 39 years (range, 21-66 years). Patients were hospitalized during therapy. On the first day, 2 g/m2 cytarabine was given, followed on days 2-5 by 60 mg/m2 etoposide, 500 mg methylprednisolone, and 25 mg/m2 cisplatin. After two cycles of chemotherapy clinical efficacy was assessed by clinical examination, chest radiography, ultrasonography and/or computed tomography. The complications were assessed on the basis of the WHO criteria. Nine patients (28.1%) had a complete response (CR), and 8 (25%) had partial response (PR). In responders, the median duration of remission was 6 months. By the end of the first year, 27% of the patients were still disease-free, and 66% were alive. High serum levels of lactate dehydrogenase had an adverse effect on disease-free survival (DFS), but no effect on overall survival (OS). The only unfavorable prognostic factor for OS was the presence of bulky disease. Neutropenia developed in 59% of patients, and febrile neutropenia developed in 74% of these patients, requiring hospitalization for an average of 8 days. Three patients died of neutropenia-associated sepsis despite broad-spectrum antibacterial and antifungal treatment. Thrombocytopenia was detected in 10 patients and anemia in three patients; among these, seven patients with thrombocytopenia and one patient with anemia required transfusions. The modified ESHAP regimen induced remission in more than half of the patients with refractory or recurrent NHL. However, the duration of remission was brief. Moreover, significant myelotoxicity was common, and the risk of treatment-related death was 9%.

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Thyroid pathology among long-term survivors from Hodgkin's disease (HD)

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Purpose: As a result of the high cure rates and relatively young age of HD patients at the time of diagnosis there are many long-term survivors who