

# Hodgkin lymphoma

## 517 PREDICTIVE AND DISCRIMINATING THREE-GROUP PROGNOSTIC SCORING SYSTEM FOR STAGING HODGKIN LYMPHOMA

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**Introduction:** Hodgkin Lymphoma exhibits one of the best lymphoma prognoses. Therapeutic progresses as well as absence of updated prognostic system for Hodgkin Lymphoma make desirable the development of a new prognostic score using relevant methodology.

**Methods:** The principal outcome was 10-year overall survival, but the selected score was also evaluated with regard to 5-year event free survival. Pre-selected variables were categorized, coded 0/1/2, before study. The variables significantly associated with 10-year overall survival in multivariate analysis were retained. Summing the levels of variables, a 3-group prognostic score was finally selected considering predictive ability (Harrell, 1996). This Prognostic Score System was then evaluated on 489 patients newly enrolled. Prediction ability of the PSS were compared to known classifications.

**Results:** Four variables were associated with 10-year overall survival: age (<40 yrs =0, ≥40 yrs =1), number of involved lymphoid areas (1-2=0, 3-4=1, ≥5 =2), visceral disease (no=0, yes=1), and systemic symptoms (no = 0, yes = 1). Scores 0 and 1, 2 and 3, ≥4 were attributed to 59.7%, 30.9%, and 9.4% of the patients who had 10-year overall survival rates of 93.5%, 75.7%, and 53.4%, respectively. Compared to existing 3-group classifications, the PSS presented higher predictive and discriminating properties. It also performed nicely on the 489 patients.

**Conclusions:** PSS is a useful alternative the existing prognostic systems to classify and treat patients.

Maucourt-Boulch D, Djeridane M, Roy P, et al. Predictive and discriminating three-risk-group prognostic scoring system for staging Hodgkin lymphomas. *Cancer* 2007; 109(2): 256-64.

Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; 5: 361-87.

## 518 PROGNOSTIC SIGNIFICANCE OF CLINICAL AND PATHOMORPHOLOGICAL FEATURES IN ADVANCED HODGKIN'S LYMPHOMA

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Although the treatment of patients (pts) with Hodgkin's lymphoma (HL) at any stage of presentation is highly successful, a significant minority of pts fails primary therapy. Distinguishing clinical and pathomorphological prognostic factors might contribute to initially better selection of pts for more intensive treatment. In a cohort of 89 pts with advanced HL (CS IIB-IV) treated with ABVD regimen from 1997 to 2004, we analyzed prognostic relevance of International Prognostic Score (IPS), bulky mass, extranodal localisation (EN), >3 sites involvement, ESR >50 as well as pathomorphological features: tissue eosinophilia (Eo) and Grade (Gr) 1,2 nodular sclerosis (NS) HL. The median follow-up was 7 years (yrs). Significance was tested according to the response rate and overall survival (OS). The OS rate was 67% after 7 yrs' follow-up. Pts with IPS >3 had more progressive disease and shorter OS (OS<sub>7y</sub> 83% vs. 49%, log rank p<0.01) and no influence on event free survival (EFS) (log rank p>0.05). Pts without bulky had better OS<sub>7y</sub> compared to those with it (OS<sub>7y</sub> 88% vs 41%, log rank p<0.01), and also EFS<sub>7y</sub> (log rank p<0.01). The EN had adverse effect on OS<sub>7y</sub> (45% vs 78% for pts without EN, p<0.01) and also on EFS (log rank p<0.05). There was no difference in OS and EFS between pts with or without >3 sites involvement. ESR >50 had also negative influence on OS (54% vs 90%, p<0.01), but not on EFS (p>0.05). Pts with tissue Eo had shorter OS (53% vs 75%, p<0.05), but not significant influence on EFS (log rank p>0.05). The shorter OS had pts with NS Gr 2 (51% vs 75% in NS Gr 1), and also EFS but this difference was not significant (p>0.05). In multivariate analysis IPS and bulky mass were independent prognostic parameters (p<0.05). In advanced HL IPS>3 and bulky ultimately characterize unfavorable features. In addition EN, ESR >50, tissue Eo, NS Gr 2 also have negative impact on disease evolution. Pts with these features are at higher risk of treatment failure and might be eligible for more effective treatment.

## 519 PROSPECTIVE ANALYSIS OF FACTORS INFLUENCING INCLUSION OF 102 PATIENTS WITH ADVANCED HODGKIN LYMPHOMA IN A RANDOMIZED TRIAL FOR FIRST-LINE CHEMOTHERAPY

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**Background:** Data on factors influencing inclusion of Hodgkin Lymphoma (HL) patients in clinical trials are limited. A prospective analysis of factors predicting inclusion in a randomized trial for advanced HL was performed.

**Methods:** All patients with advanced HL referred to the Saint-Louis Hospital in the period of January/2003 until May/2007 were studied. During this period, a GELA/EORTC Randomized Trial, which compares ABVD with BEACOPP, was open for recruitment. Exclusion criteria of the ineligible patients, and the physician's reasons for non-recruitment were prospectively recorded. The reasons for patient's refusal were retrospectively collected from their records. Logistic regression analyses were performed in order to identify factors associated with inclusion.

**Results:** A total of 102 patients were diagnosed. Overall, 51% of patients were included in the trial. Seven patients were ineligible, 22 refused to participate, and 21 patients were not accrued due to the physician's decision. The main reasons for patient's refusal were standard treatment preference and concerns about experimental arm toxicity, mainly infertility risk. Conditions that could prevent accurate follow-up and toxicity concerns accounted for the majority of the reasons due to physician. The presence of B symptoms (OR=5.35, IC95% 2.12-13.47) and IPS<sup>3</sup> (OR=2.69, IC95% 1.8-6.72) were independently associated with inclusion.

**Conclusion:** Our data provides insights about trial recruitment for a disease that affects mostly young patients, whose standard treatment yields good results. Clinical trial recruitment must be encouraged and the understanding of these factors might improve tools to improve it.

## 520 CLASSICAL HODGKIN LYMPHOMA, LYMPHOCYTE DEPLETED TYPE: CLINICOPATHOLOGICAL ANALYSIS IN 28 CASES AND COMPARISON WITH OTHER TYPES OF CLASSICAL HODGKIN LYMPHOMA

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**Introduction:** Lymphocyte depleted type (LD) is a morphological subtype of classical Hodgkin lymphoma (CHL) but its rarity and heterogeneous morphological character makes definite clinicopathological identification difficult. To overcome these problems, we reviewed CHL cases and analyzed LD cases with the morphological features of diffuse fibrosis type.

**Material and Methods:** Among 310 CHL cases, 29 cases were diagnosed as LD. We could additionally analyze clinical data of 157 CHL cases (including 28 LD cases) and immunophenotype of 150 CHL cases (including 28 LD cases). We compared clinicopathologic data between LD cases and other type CHL cases and determined prognostic factors by univariate and multivariate analysis.

**Results:** All of the cases diagnosed as LD showed the following morphological features: 1) Diffuse non-collagenous fibrosis without nodular structures highlighted by Ag staining. If nodular structures were detected, they were diagnosed as NS. 2) Only a few HRS cells (non sheet-like) in whole section. 3) Depleted reactive lymphocytes with infiltration by numerous histiocytes and fibroblasts. These morphological findings are compatible with new WHO classification and previous reports. LD showed more progressive disease stage (Stage 3/4, 64%) than other type CHL (Stage 3/4, 30%; P<0.001), more frequent B symptoms (89% vs. 40%; P<0.001) and extranodal invasion (50% vs. 11%; P<0.001), older age (median: 66 vs. 33; P<0.001), higher serum soluble interleukin 2 receptor levels, (median:8240U/ml vs. 1705 U/ml; P<0.001), and much poorer prognosis regardless of IPFP score (five-year overall survival: 29% vs. 86%; P<0.001). The morphological subtype of LD represented an independent prognostic factor as did age and IPFP score by multivariate analysis. Immunohistochemistry showed that the characteristics of Hodgkin and Reed-Sternberg (HRS) cells of LD are basically not different from those of other types CHL in terms of CD30, CD15, and chemokine receptors, except for high-level EB-virus infection (72% vs. 41%; P=0.002).

**Conclusions:** LD should be distinguished from other types of classical Hodgkin lymphoma because of its definitive clinicopathological characters.

Prognostic factor	Univariate P-value	Multivariate RR(95% confidence interval)	P-value	RR(95% confidence interval)	P-value
Histology:LD	<0.0001	3.45 (1.32-9.00)	0.012	5.37 (2.19-13.18)	0.002
Age > 45 years	<0.0001	6.17 (1.67-22.72)	0.006	-	-
Stage III/IV	0.0009	1.637 (0.63-4.27)	0.31	-	-
B symptom(+)	0.0017	2.21 (0.68-7.19)	0.19	-	-
EBV (+)	0.051	1.03 (0.43-2.51)	0.95	-	-
IPFP score >3	<0.0001			5.55 (2.25-13.70)	0.002

**521 CORRELATIONS BETWEEN ELEVATED SERUM FERRITIN LEVEL AND INITIAL CHARACTERISTICS OF HODGKIN'S LYMPHOMA PATIENTS**

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**Introduction:** Ferritin, identified as a Hodgkin's lymphoma (HL) specific antigen, constitutes a target of radioimmunotherapy (Decaudin et al., Anticancer Drugs 2007; 18: 725). However, very few data are available on correlations between serum ferritin level and characteristics of HL patients (pts).

**Patients and methods:** Forty-five pts treated at the Institut Curie between 2000 and 2007 were included in the study.

**Results:** Initial pts characteristics were: 39 nodular sclerosis type HL (82%); Male/Female sex ratio 1.1; age >45 years 18%; PS >1 9%; B symptoms 49%; extranodal involvement 38% including 9 bone marrow dissemination; stage III,IV 51%; ESR ≥ 30 59%; haemoglobin level <10.5 g/dl 22%; blood leucocyte count ≥15 10<sup>9</sup>/l 18%; blood lymphocyte count <0.6 10<sup>9</sup>/l in 1 pt; albumin level < 40 g/l 40%; International Prognostic Score ≥3 32%; and elevated serum ferritin level 31%. After the first line of treatment, 39 pts were in complete remission (87%) and 1 in partial remission. With a median follow-up of 35 months, 4 pts relapsed and 3 pts dead. Elevated serum ferritin level was correlated with an age lower than 45 years (p=0.04), the presence of B symptoms (p<10<sup>-4</sup>), an extranodal involvement (p=0.07), a stage IV (p=0.01), and an ESR greater than 30 (p=10<sup>-3</sup>). Because of the small number of events (relapses or deaths), the prognostic impact of elevated serum ferritin level could not be evaluated.

**Conclusions:** High serum ferritin level was observed in a third of HL pts at initial diagnosis and was mainly associated with pejorative characteristics of the disease.

**522 METALLOTHIONEIN (MT) EXPRESSION PROFILING IN HODGKIN'S LYMPHOMA: IDENTIFICATION OF A MOLECULAR BIOMARKER FOR THE SUBCLASSIFICATION OF PATIENTS**

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**Introduction:** Metallothionein (MT) is an antioxidant metalloprotein with mounting roles in human pathology. MT is rapidly induced by numerous stressors, pathogens and cytotoxic agents, which indicates its role in cellular survival, proliferation and host defense mechanisms. Thus, MT induction by heavy metals or anti-cancer agents (chemotherapy, radiation) is directly linked to its protection against genotoxicity, oxidation by radicals and apoptotic cell death. Thus, MT confers survival mechanisms associated with resistance to anti-cancer treatment and a poor survival rate, as shown in various human neoplasias. MT expression and prognostic value were characterized in non-Hodgkin lymphomas and leukaemias but not in Hodgkin's lymphoma (HL).

**Methods:** We analyzed MT expression in lymph nodes from 35 HL patients (13 nodular sclerosis (NSHL), 14 mixed cellularity (MCHL), 5 lymphocyte-rich classic HL (LRCHL), and 3 nodular lymphocyte predominant HL (NLPHL) patients) and 10 controls. The data were correlated to histopathological and clinical parameters.

**Results:** MT expression was significantly changed in HL relative to controls. The MCHL and NSHL showed qualitative and quantitative MT alterations with numerous intensely stained MT positive cells. In NLPHL MT was moderately and focally increased; whereas in LRCHL, MT was depleted. The controls showed mild MT staining in the stroma (the capsule). In HL MT was mainly expressed by reactive cells (like myelomonocytes, macrophages, granulocytes), as Hodgkin and Reed-Sternberg cells and L&H (popcorn) cells were devoid of MT. In NSHL MT also increased in fibrous cells and vessel walls.

**Conclusion:** HL subgroups show distinct MT expression profiles indicating that MT may provide a molecular biomarker for HL subclassification as well as MT may reflect the patient's response to therapy and clinical prognosis.

**523 DOES BULKY MEDIASTINAL DISEASE AT DIAGNOSIS INFLUENCE OUTCOME IN ADULT UNFAVOURABLE EARLY STAGE HODGKIN LYMPHOMA?: UNICENTRE RESULTS OF A PROSPECTIVE STUDY ABOUT 54 TUNISIAN PATIENTS**

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**Introduction:** It is common in Europe to subdivide early stage Hodgkin lymphoma (HL) into favourable and unfavourable (intermediate) according to certain risk factors. In the Tunisian prospective study, the EORTC risk factors are used to stratify our early-stage Hodgkin lymphoma.

**Aim:** to assess the influence of bulky mediastinal mass as compared with other risk factors on outcome in early unfavourable HL.

**Patients And Methods:** 54 patients with unfavourable HL were enrolled in the Tunisian adult HL study. Median age was 32 years, sex-ratio 0.86. 50 patients stage II and 70% had more than 3 involved lymphnode regions. 20 patients (37%) met the criteria for mediastinal bulky mass. 15 patients (27%) had peripheral bulky mass. Erythrocyte sedimentation rate (ESR)<sup>3</sup> 50mm/h without or <sup>3</sup> 30mm/h with B was seen in 68% of patients. All patients were treated with 6 ABVD and 36 Gy involved fields radiotherapy. Last prognostic factors had been analyzed with regard to their impact on response and ehec rates, overall survival (OS), event free survival (EFS) and relapse free survival (RFS).

**Results:** After 6 cycles 45 patients (83.3%) showed a complete response and the primary failure rate was 16.7%. After a median follow-up of 34 months 2 patients had relapsed and 3 had died (progressive disease). OS and EFS rates at 05 years were 94% and 81% respectively. The only significant adverse prognostic factor was the presence of bulky mediastinal disease. Significant differences were found in the primary failure rate (40% vs 2.9%, p=0.01), in the 5 years OS (85% vs 100%, p=0.01) and in EFS (60% vs 94%, p:0.001) But non significant difference regarding RFS (100% vs 94%, p=0.3).

**Discussion:** Our study confirms the adverse prognostic factor of bulky mediastinal disease among early HL. In North America and in Germany, the most groups have included those patients under the heading of advanced HL. Intensified chemotherapy (escalated BEACOPP) as first treatment rather than ABVD predicts a better survival but expose patient to a major late toxicity.

**524 RADIATION THERAPY OF INITIALLY INVOLVED ZONES WITH MODIFIED MULTIFRACTIONATION OF A DOZE IN THE COMBINED TREATMENT OF PATIENTS WITH HODGKIN'S LYMPHOMA**

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**Introduction:** the purpose of research is the effectiveness increase of the combined treatment of primary patients with Hodgkin's lymphoma by application of the involved zones irradiation using modified regimen of doze multifractionation.

**Methods:** from 2003 to 2006, 83 patients with Hodgkin's lymphoma (stages I-IV) received the primary combined treatment with application of the involved zones irradiation using modified regimen of doze multifractionation with single dose 1.2 Gy twice a day with interval 4 hrs and with total dose 36 Gy. The chemotherapy in ABVD and BEACOPP regimens was applied before irradiation.

**Results:** the objective response has been reached in 78 (94.0%) patients. Progressing during primary treatment was observed in 5 (6.0%) cases. The 2.5-year relapse rate was 3.6% (3 patients). Comparing the received results with data from earlier studies of accelerated hyperfractionated irradiation (AHF) of the involved zones with the single dose of 1,35 Gy twice a day, cared in clinic, the rate of radiation pneumonitis was 17.7% and 13.1% (δ=0.3) respectively. Reduction of irradiated volumes resulted in decreased rate and severity of hematological complications: leucopenia of IV degree and thrombocytopenia of III-IV degree were not observed, the rate of leucopenia of III degree significantly decreased (5.0% compared to 51.7% in AHF).

**Conclusions:** irradiation of the involved zones in modified regimen of doze multifractionation is an effective treatment option, which results in lower rate of radiotherapy complications in patients with Hodgkin's lymphoma. The method is

easily reproduced and shows economical benefits by shorter length of hospital stay and decreased rate of hematological complications.

### 525 DOUBLE AUTOGRAFT APPROACH IN HEAVILY PRETREATED HODGKIN'S LYMPHOMA PATIENTS

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**Background:** About 25% of Hodgkin's lymphoma (HL) patients (pts) relapse or do not respond to first line therapy. Dose intensification followed by autologous stem cell support (ASCT) is the standard approach for these pts. Aim of our report was to analyze the feasibility and efficacy of a double ASCT in heavily pretreated HL pts.

**Methods:** Five pts (3M/2F) received a tandem transplant. Median age at transplant was 32 years (range 19-35) and the median interval from diagnosis to first ASCT was 53 months (12-102); all pts had received at least 2 therapy lines pre-ASCT. Preparative regimens consisted of BEAM and Mel200 in 3 cases, BEAM/BEAC in 1 case and sequential Mel200 in the last pt.

**Results:** The median number of CD34+ cells reinfused/kg was 3.11 (2.09-7.5) and 3.68 (2.84-6), respectively for the first and second ASCT. The median time to ANC recovery  $>0.5 \times 10^3/L$  was 11 (9-14) and 10 (9-13) days, respectively; PLTS reached  $50 \times 10^3/L$  after a median of 17 (13-18) and 18 (9-26) days, respectively. The median interval between the first and second transplant was 3 months (range 2-4). No grade II-IV organ toxicity was recorded and there were no transplant-related deaths. The median hospitalization time was 20 (15-22) and 15 days (14-23), respectively, for the first and second course. Pt 1, with progressive disease (PD) after 5 lines of therapy, is free from progression (FFP) at 84 months from ASCT; pt 2, in PD after 3 lines of therapy, is FFP 14 months after ASCT; pt 3, who had failed 2 lines of therapy, is FFP 11 months from ASCT; pt 4, in PR after a 3<sup>rd</sup> line of treatment, is in CCR at 6 months; pt 5, in PR after 5 lines of therapy, who received a double course of high-dose melphalan because of cardiac failure, is in CCR 3 months off-therapy.

**Conclusions:** A double autograft is a feasible and effective procedure for advanced heavily pretreated HL and is well tolerated also in pts with poor performance status; in addition, the tandem transplant can be successfully performed without delay. This approach represents an alternative therapeutic option for pts who are often offered more demanding treatment programs like allogeneic transplantation.

### 526 GEMCITABINE, IFOSFAMIDE, OXALIPLATIN AND RITUXIMAB (R-GIFOX), A NEW EFFECTIVE SALVAGE REGIMEN FOR RELAPSED AND REFRACTORY HODGKIN AND NON-HODGKIN'S LYMPHOMA: RESULTS OF A PILOT STUDY

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**Background:** We evaluated for activity and toxicity a new salvage regimen combining Gemcitabine (G) and Oxaliplatin (Ox), with Ifosfamide (Ifo) and Rituximab (R) (R-GIFOX), in patients (pts) with recurrent Hodgkin Disease (HD) and Non-Hodgkin's Lymphoma (NHL).

**Patients and methods:** Pts were scheduled to receive 3 R-GIFOX courses followed by mobilization and ASCT or by 3 more courses if ineligible for ASCT. R-GIFOX consisted of R 375 mg/m<sup>2</sup> d1, G 1000 mg/m<sup>2</sup> d2, Ox 130 mg/m<sup>2</sup> d3 and Ifo 5 g/m<sup>2</sup> on d3, as a 24-hour single infusion or fractionated over days 3-5 for pts aged  $>65$ , every two weeks with G-CSF support (5 mcg/kg/d or 10 mcg/kg/d after the 3<sup>rd</sup> course for stem cells mobilization). Responses were evaluated by the integrated FDG-PET/IWC criteria, after the 3<sup>rd</sup> course and at the end of the entire program.

**Results:** Forty-two pts (median age 62 yrs, r 21-79) with relapsed (n=27) or primary progressive (n=15) aggressive [diffuse large B cell/follicular G3 (n=22), mantle cell (MCL) (n=11)] NHL and HD (n=9) were accrued. Stage IV: 74%; bulky disease: 24%;  $>1$  E-sites: 36%; previous treatments: median 1, range 1-4. All the pts completed at least 3 courses (median 6, r. 3-6) and were evaluable for response. The ORR after 3 courses was 83%, with 30 complete and 5 partial responses. Interestingly, high CR rates were achieved among HD (n=7; 78%) and MCL (n=10, 91%). CRs were 59% for diffuse large cell/follicular G3 NHL pts. Stem cell mobilization was obtained in 11 eligible pts. Bad mobilizers occurred in case of previous irradiation or  $>2$  treatments. Grade 3 and 4 thrombocytopenia was documented in 42% of pts, febrile neutropenia and infections were uncommon, grade 3 peripheral neurotoxicity rare. Failure free survival was 63% for the whole group of pts at median follow up of 25 months (r. 4-42). Molecular remissions were documented in pts with MCL.

**Conclusions:** R-GIFOX regimen was active and displayed a favorable profile of toxicity in recurrent lymphoma, especially in HD and MCL patients. It can offer, even older patients, an intensive but less toxic alternative to cisplatin-based chemotherapy.

### 527 BEACOPP REGIMEN IN ADVANCED HODGKIN'S LYMPHOMA: PRELIMINARY RESULTS

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**Background:** About 25% of Hodgkin's lymphoma (HL) patients (pts) relapse or do not respond to first line therapy. No data are available on the efficacy of the BEACOPP regimen in relapsed/refractory HL pts.

**Methods:** We retrospectively evaluated two groups of relapsed pts: **group A** pts (10) were previously treated with ABVD and RT receiving BEACOPP in first relapse; **group B** pts (13) received ABVD and underwent HDT after relapse (8 pts) or refractoriness (5 pts); they received BEACOPP regimen after HDT. At diagnosis the median age was 30 and 31 years in group A and B respectively, M/F ratio was 3/7 and 8/5, 5 and 7 pts had bulky disease, respectively; all pts had advanced stage.

**Results:** **Group A:** The median time from ABVD to relapse was 9 months (range 4-65). Nine CR and 1 PR were obtained after BEACOPP treatment (6-8 cycles based on previous therapy). After a median follow-up of 29 months 5 pts (50%) are alive in second CR, 3 pts relapsed after 12, 12 and 16 months, respectively, and are in third CR after HDT, 1 patient (PR after BEACOPP) is alive with disease and 1 patient died in CR due to a secondary leukaemia. **Group B:** 1 patient was treated while refractory to HDT and 12 received BEACOPP (4-8 cycles based on previous therapy) in relapse, (occurred after a median of 10 months (range 4-43) from HDT. Eight pts (62%) obtained a CR, 1 a PR, 2 were refractory and 2 have died of toxicity (sepsis during neutropenia). To date, 8 pts (62%) are alive: 4 (31%) in CR 36, 39, 42 and 52 months from BEACOPP, respectively, 3 (23%) with disease at 3, 31 and 54 months from BEACOPP and 1 pt is in 4<sup>th</sup> CR 12 months from allograft; 5 pts (38%) have died. All pts experienced hematologic toxicity (WHO 3-4) with 2 deaths due to septic shock. One aspergillary pneumonia, 1 acute pericarditis, 2 congestive heart failures and 3 aseptic osteonecroses caput femoris were observed.

**Conclusions:** These preliminary results show a high efficacy of the BEACOPP regimen in CR induction (100%) and duration (50% at a median follow-up of 29 months) as 2<sup>nd</sup> treatment for HL pts. This regimen should also be considered for the very poor prognosis population relapsing after HDT.

### 528 TWO CYCLES OF ESCBEACOPP FOLLOWED BY FOUR CYCLES OF ABVD IS AN EFFECTIVE REGIMEN FOR ADVANCED HODGKIN LYMPHOMA PATIENTS WITH HIGH IPS SCORE

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**Background:** It is well recognized that escalated (esc) BEACOPP regimen is superior to COPP-ABVD for pts in advanced stage Hodgkin's lymphoma (HL) who have a poor IPS. In an attempt to reduce the toxicity of the original schedule, while preserving improved initial tumor control in this high risk group of pts, we conducted a phase II study, employing the combination of fewer cycles of escBEACOPP followed by ABVD.

**Methods:** Newly diagnosed HL pts, with unfavorable stage IIB or stages III-IV with IPS $\geq 3$  were received two cycles of escBEACOPP followed by reevaluation with PET/CT scans. If a CR or PR was achieved, pts continued to receive four cycles of ABVD, while those pts who failed to reach this status received salvage therapy.

**Results:** Since 2001, 45 eligible pts received this regimen. Following the first two cycles of escBEACOPP the overall response rate (CR+PR) was 100% and at the end of all therapy 40 (89%) pts were in CR, 3 (7%) in PR, while 2 (4%) pts had progressive disease. After a median follow-up of 38 months (range 8-73), progression free survival (PFS) and overall survival at 3 years were 79% and 97%, respectively. These survival rates are higher than those expected for ABVD containing regimens and comparable with the estimated long term survival rates reported for the poor prognostic subgroup of pts, who had received eight cycles of escBEACOPP. Furthermore, the 3-year PFS for early PET negative pts (n=31) and early PET positive pts (n=13) was 86% and 52%, respectively (P=0.01). In terms of treatment failure, the positive predictive value of early PET was only 30%, while the negative predictive value was 96%.

**Conclusions:** combined escBEACOPP-ABVD therapy is well tolerated and may improve the outcome in pts with advanced HL who have high IPS scores. While the positive predictive value of early PET was lower than expected, the results of early PET still have a significant long term prognostic role in the treatment of pts receiving this regimen.

### 529 COMBINATION OF THE ANTI-CD30- AURISTATIN-E ANTIBODY-DRUG CONJUGATE SGN-35 WITH CHEMOTHERAPY IMPROVES ANTITUMOR ACTIVITY IN HODGKIN'S LYMPHOMA

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Despite improvements in long term survival rates of patients with Hodgkin lymphoma (HL) treated with combined modality therapy (abbreviated chemotherapy and limited irradiation), new strategies to further improve outcome and reduce therapy-induced complications are needed. The antibody-drug conjugate (ADC) SGN-35 consists of the tubulin inhibitor monomethyl auristatin E (MMAE) conjugated to the anti-CD30 monoclonal antibody cAC10. This ADC potentially interferes with the growth of CD30 positive hematologic tumors, including HL and anaplastic large-cell lymphoma (ALCL). Here we report SGN-35 localized into tumor xenograft in mice and shows potent antitumor activity in mice models of HL either alone or in combination. When combined with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), or gemcitabine, the antitumor activity was markedly better than was observed with either SGN-35 or chemotherapy only regimens. Combination treatment was not associated with alterations in CD30 expression on tumors. Improved antitumor activity was also observed in high tumor burden models, indicating that combining SGN-35 with chemotherapeutic agents such as gemcitabine may be advantageous for the treatment of patients with relapsed or refractory HL.

### 530 PROMISING EFFECT OF BORTEZOMIB TREATMENT IN HODGKIN'S LYMPHOMA

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**Introduction:** Hodgkin's lymphoma forms less than 1% of all de novo neoplasm and account for approximately 30% of all lymphomas. Despite its well known histological and clinical features, the search for more effective ad hoc strategies in selected cases with poor response to conventional treatment is necessary. Bortezomib (PS-341), protease inhibitor, has shown promising effect in treatment of variety cancers (plasma cell myeloma, pancreatic cancer etc.). In Hodgkin's lymphoma the supposed mechanism of action is by inhibition of the degradation of IκB and thereby inhibition of the NFκB activation. The main bortezomib improvement is the potentiation of another anticancer drugs or in enhancing of chemosensitivity of cancer cells.

**Material and Methods:** We have analysed main molecular pathways in 4 different cell lines (L-540, L-428, L-1236, KM-H2) derived from Hodgkin's lymphoma after exposition to bortezomib treatment alone or in combination with commonly used cytostatics.

**Results:** Regarding to p53 status we found very interesting differences in ability to activation of p21 protein, regulation of MDM2 level, NFκB level etc. Our results show bortezomib-induced apoptosis slightly dependent on p53 status in all analysed cell lines. Unexpectedly we have no effect on heat shock protein (HSP 90) level.

**Conclusions:** We proved the impact of bortezomib treatment on Hodgkin's lymphoma cell lines in several molecular pathways resulting in cell death by the way of apoptosis. Our results suggest the prospective use of bortezomib in Hodgkin's lymphoma treatment most importantly in combination with standard treatment protocols.

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### 531 A PHASE I EVALUATION OF BORTEZOMIB IN COMBINATION WITH ICE (BICE) AS TREATMENT FOR RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA

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**Background:** The proteasome inhibitor bortezomib induces cell cycle arrest and apoptosis of Hodgkin lymphoma (HL) cells. We have shown that single-agent activity of bortezomib in heavily pretreated HL patients was not significant, however preclinical data has demonstrated that bortezomib may synergize with chemotherapy. Thus, this study evaluates the combination of bortezomib plus ICE chemotherapy in patients with relapsed/refractory HL.

**Methods:** Eligibility: 1) Only 1 prior chemotherapy regimen, 2) No prior ASCT. Regimen: ICE (Moskowitz, C et al. 2001). Bortezomib on D1 and D4 at dose levels of 0 = 1.0 mg/m<sup>2</sup>, 1 = 1.3 mg/m<sup>2</sup>, and 2 = 1.5 mg/m<sup>2</sup>. Neulasta given on D5. Cycles repeated on D14 if platelet count is ≥100,000/mm<sup>3</sup> and ANC is ≥1,000/mm<sup>3</sup>. After 3 cycles response is evaluated by CTs and PET/CT. Hematologic DLT is grade 4 thrombocytopenia or neutropenia lasting greater than 2 weeks.

**Results:** Median age is 32. 13 patients enrolled (7 primary refractory, 6 relapsed). 3 patients each at dose levels 0 and 1, 7 patients at dose level 2. 10 patients were evaluable

for toxicity and 11 patients for response. By 1999 Cheson response criteria there are 3/11 CRs, 5/11 PRs, and 3/11 PDs. All patients with PD were primary refractory patients. PET/CT scans were negative for 8/11 patients and thus by 2007 revised Cheson response criteria 8/11 patients achieved CR. 7/8 patients who responded underwent ASCT (1 patient declined ASCT). Treatment was well tolerated with no DLTs noted. Reversible grade 4 neutropenia and thrombocytopenia occurred respectively in 40% and 50% of patients. Median day for retreatment for cycle 2 was D20 and for cycle 3 was D21. There have been no toxicities of peripheral neuropathy, febrile neutropenia, or infection.

**Conclusions:** Our preliminary data suggest safety and efficacy of bortezomib plus ICE in relapsed/refractory Hodgkin's lymphoma patients. These results support further evaluation of this combination as salvage treatment for Hodgkin lymphoma in a randomized phase II study.

### 532 QUALITY OF LIFE (QOL) IN LONG-TERM SURVIVORS OF HODGKIN LYMPHOMA (HL) TREATED WITHIN THE GERMAN HODGKIN STUDY GROUP (GHSG) IN THE CZECH REPUBLIC: A CROSS-SECTIONAL STUDY OF PATIENTS TREATED 1995 TO 2003

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**Introduction:** We investigated the current QoL in long-term survivors of HL treated within the GHSG between 1995 and 2003 in the Czech Republic. The aim was to describe patients (pts) QoL after cure and returning to normal life during the years (yrs) after end of treatment in a cross-sectional design.

**Patients and Methods:** EORTC QLQ C-30, MFI-20, subjective retrospective evaluation of treatment and a life situation questionnaire (LSQ) were used for the assessment of the pts' situation after end of treatment. An authorised Czech version of the questionnaires was sent to 172 pts who were followed-up for four and more yrs.

**Results:** 142 (82.5%) pts replied. Median age at time of assessment was 33 yrs, median follow-up 66 months. Regarding the QoL functional and fatigue scales, pts report a mixed pattern of responses but indicate quite severe limitations in their perceived QoL during later years of follow-up. Emotional functioning and global QoL recovers fully only in 50% of pts 4-12 years after end of treatment and about 25% report constant severe strain. General fatigue remains high with 45% of pts reporting 'high fatigue' levels but only 15-30% of pts report high levels of reduced motivation and activity. In physical functioning 70% recover fully and only 6% report very low functioning. In general, women report lower QoL and higher symptom scores over time than men.

**Conclusions:** QoL data from the reintegration process of pts into normal life during the yrs of follow-up reveal substantial strain and limitations of QoL, particularly in subsets of patients and in specific areas of QoL. Longitudinal QoL assessment within the GHSG is ongoing also for Czech pts and will add the QoL course of recovery to the current cross-sectional data. RESULTS regarding also socio-demographic variables will be included in the final presentation.

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### 533 QUALITY OF LIFE AND FATIGUE IN HODGKIN'S LYMPHOMA PATIENTS

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**Introduction:** Quality of life of Hodgkin's lymphoma (HL) patients is determined by their disease itself, its treatment and the complications of the therapy.

**Methods:** We determined the quality of life and frequency and severity of fatigue in 168 Hodgkin's lymphoma patients (85 women, 83 men), who were treated with HL at our department. We used the EORTC QLQ-C30 questionnaire and determined global health status and fatigue in all patients. We scored all functional and symptom scales in cured patients (who were in complete remission for at least 10 years, mean period of survival after the treatment(s) was 16.61 years) and who suffered from late complications. Median age was 43.11 years at the time of the examination.

**Results:** Global health status score (QL2) was significantly lower in patients who had late complications (mean QL2: 45.53, patients with no complications QL2: 67.57, p<0.001) and in cured patients (mean QL2: 52.5 vs who were after the treatment within 10 years, or who were treated actively mean QL2: 67.48, p<0.001). We found that fatigue level was significantly higher in patients who were treated more than 20 years ago/ fatigue score (FA): 53.37, during treatment FA: 29.35 (p<0.03). Significantly higher FA was observed in patients who suffered from late complications of the treatment (FA: 48.72, no complications FA: 31.88, p<0.001). We didn't find any associations between each of these complications and fatigue. Those patients who were in complete remission for at least ten years had significantly higher FA than those ones, who were not cured. In the group with complications the physical (PF), role, and emotional

functioning was significantly lower, dyspnoea and pain score was significantly higher than the group without complications. PF was lower, dyspnoea score was higher in the cured group in contrast to not cured group.

**Discussion:** More co-morbidity (cardiovascular disease, hypothyroidism etc.) can cause higher fatigue score that observed in these groups of HL patients. Fatigue is more frequent than we think it, and has a strong effect on quality of life, so its early recognition and treatment is important and needs multidisciplinary cooperation.

### 534 HODGKIN'S LYMPHOMA WITH PRIMARY MANIFESTATION IN THE LIVER

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**Introduction/background.** Hodgkin's lymphoma (HL) is one of the most curable cancers in adulthood. HL can be cured in 85-95% of all cases with modern treatment strategies, regardless of clinical stage and histologic types. HL rarely (in 5-8% cases) manifests primarily in liver. The liver HL clinically presents with upper right abdominal quadrant pain, weight loss, night sweat, hepatosplenomegaly, pruritus associated with cholestasis and high bilirubin level, coagulopathy. Frequently, the rapid course of HL with progression to acute liver failure prevents its treatment; moreover, its progression leads to MODS and death.

**Material and methods.** We analyzed retrospectively the incidence and outcome of primary hepatic involvement in patients (pts) with HL treated in our centre in 1995-04/2007.

**Results.** The extranodal disease of HL was diagnosed in 122 (37.5%) of 325 pts with intermediate or advanced stage HL (summary 346 pts with HL). The liver was affected in 7 (2.2%) pts; the liver localization of HL was diagnosed at the time of diagnosis in 5 pts in one patient during the course of radiotherapy after chemotherapy and in one patient on autopsy. The median age was 42 years (17-51), M/F was 6/1, histological type: mixed cellularity in 5 pts, lymphocyte-predominant in one patient and nodular sclerosis in one patient, the median IPS was 4. The hepatic biopsy was performed in 6 pts: the liver involvement of HL along with intrahepatic cholestasis was recorded in 4 pts, the vanishing bile duct syndrome was recorded in one patient and idiopathic cholestasis was recorded in one patient. Six pts were treated with combined chemotherapy (COPP, BEACOPP, VBL-PDN). The chemotherapy was not initiated in one patient due to poor condition. Only one patient is still alive (in complete remission), 6 pts died in the initial phase in spite of intensive complex supportive care.

**Conclusion.** Our results are in agreement with literature data. The prognosis of patients with primary liver manifestation of HL is unfavorable. The results might be improved by early diagnosis and targeted therapy.

### 535 AN EARLY RELAPSE OF HODGKIN'S LYMPHOMA THAT IS DEMONSTRATED AS A PARANEOPLASTIC CEREBELLAR DEGENERATION

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**Background:** Paraneoplastic cerebellar degeneration (PCD) represents the most described paraneoplastic neurological syndrome occurring, in addition to Hodgkin's lymphoma (HL), especially at small cell lung cancer and ovary cancer. We always have to distinguish a primary infiltration of CNS by imaging and examination of the liquor, which is at HL very rare (incidence of 0.2%) and means a late symptom of an already advanced disease with a worse prognosis.

**Material and methods:** In 11/2005 a 30-year-old man was diagnosed with nodular sclerosis HL stages II B at our clinic. The pt was treated with 4 cycles of the chemotherapy ABVD and the IF radiotherapy (30 Gy) of the retroperitoneum and the mesenteric lymph nodes. According to the CT scan a complete remission was achieved. After 11 months the pt was hospitalized for a gradually progressive ataxia, vertigo, dysarthria and nystagmus. Imaging of CNS including MRI and the cytology of the liquor was negative. By the CT scan the mediastinal lymphadenopathy was found out and completing FDG-PET examination confirms the suspicion for a relapse of HL, which was eventually confirmed by the thoracoscopy.

**Results:** With regard to an early relapse of HL salvage chemotherapy DHAP was indicated. Yet after the 1st cycle a distinctive regression of the neurological symptoms which, consequently, went off completely. After the 2nd cycle of the chemotherapy a successful separation of the PBSC came through. Afterwards, the pt took high-dose chemotherapy BEAM with an autologous PBSC support (10/2007). Considering CT scan examinations including whole body FDG-PET showed a complete remission again.

**Conclusions:** The occurrence of an early relapse of HL carried out by the symptoms PCD is presented in the case report. Differential diagnostics can be facilitated by the identification of the HL specific paraneoplastic anti-Tr antibodies (named after its inventor J. Trotter in 1976), that are made against Purkinje cells in the cerebellum. Their determination in the time of the relapse of our patient was impossible because of the inaccessibility of this method in the Czech Republic.