Hodgkin lymphoma

282 NODULAR SCLEROSIS-TYPE CLASSICAL HODGKIN LYMPHOMA IN THE ELDERLY: POOR PROGNOSIS AND HETEROGENEOUS NATURE

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Background: Classical Hodgkin lymphoma (CHL), which is characterized by the presence of Hodgkin and Reed Sternberg (HRS) cells in a background of non-neoplastic inflammatory cells, is divided into four histological subgroups, nodular sclerosis (NSCHL), mixed cellularity (MCCHL), lymphocyte-rich, and lymphocyte depletion. While NSCHL in young adults is characterized by a mediastinal mass and good prognosis, the clinicopathological characteristics of NSCHL in the elderly (NSCHL-e) remain uncertain.

Materials and Methods: 792 CHL cases in the multicenter study group of Hodgkin lymphoma in Japan were enrolled for the present study. To better characterize NSCHL-e, we compared the clinicopathological profiles of 84 NSCHL-e patients (≥50 y.o.) with 237 NSCHL-y patients (<50 y.o.).

Results: NSCHL-e patients were characterized by male predominance and a more advanced clinical stage (53%) than NSCHL-y. Immunophenotypically, NSCHL-e cases showed a significantly higher rate of CD20-positive (24%), granzyme B(graB)-positive (14%) and EBER-positive cases (39%) than NSCHL-y. The prognosis of NSCHL-e was poorer than that of NSCHL-y ($P < 0.001$). But when CD20-positive and graB-positive cases are excluded from NSCHL-e, there is no significant difference in survival between elderly and young NS cases.

Conclusion: NSCHL-e is characterized by an unfavorable prognosis and different clinicopathological features when compared to NSCHL-y, which is considered as typical NSCHL. Some of NSCHL-e cases had atypical phenotypic HRS cells, namely CD20-positive, graB-positive, and EBV-positive ones. NSCHL-e with atypical phenotype might be associated with the gray zone lymphoma, in which CD20-positive NSCHL-e is roughly equal to the borderline cases between B-cell lymphoma and CHL. GraB-positive NSCHL-e is similar to T-cell lymphoma with HRS cells. EBER-positive NSCHL-e might be categorized as MCCHL with marked fibrosis. As mentioned above, the resistance to chemotherapy (including ABVD) in NSCHL-e can be explained by the heterogeneous nature of Hodgkin and Hodgkin-like lymphomas.

Table Clinicopathological characteristics between NSCHL in the elderly (NSCHL-e) and NSCHL in the young adults (NSCHL-y).

	NSCHL-e (n=84)		NSCHL-y(n=237)		P §
Sex (male/female)	63/21		116/121		<0.0001
Age(y), median(range)	65 (50-86)		27 (9-49)		-
PS >1	10	(18%)	19	(12%)	0.32
Stage III/IV	41	(53%)	70	(32%)	0.001
B symptoms	32	(41%)	74	(34%)	0.29
Extranodal >1site	6	(8%)	19	(9%)	0.74
BM involvement	4	(5%)	10	(5%)	0.85
LDH >normal	40	(63%)	94	(53%)	0.14
Immunophenotype					
cyCD3	3/36	(8%)	4/79	(5%)	0.50
CD15	50/78	(64%)	145/219	(66%)	0.74
CD30	73/79	(92%)	208/219	(95%)	0.40
CD20	13/54	(24%)	12/155	(8%)	0.001
EBV	29/75	(39%)	14/207	(7%)	<0.0001
Granzyme B	8/57	(14%)	5/142	(4%)	0.007

Abbreviations: NSCHL-e: nodular sclerosis type classical Hodgkin lymphoma in the elderly; NSCHL-y: nodular sclerosis type classical Hodgkin lymphoma in the young adults; PS: performance status; BM: bone marrow.

§ NSCHL-e versus NSCHL-y

283 ABBREVIATED 8 WK CHEMOTHERAPY (CT) + INVOLVED NODE RADIOTHERAPY (INRT) FOR NON-BULKY STAGE I-II HODGKIN LYMPHOMA: PRELIMINARY RESULTS OF THE STANFORD G5 STUDY

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Introduction: Combined modality therapy (CMT) is the standard of care for non-bulky Stage I-II HL. Currently, brief CT +30 Gy involved field (IF) radiotherapy (RT) is associated with a high cure rate. To further limit treatment risk, we tested a reduced intensity approach consisting of brief CT (Stanford V–C x 8 weeks) + RT 20 Gy INRT (G5 study).

Methods: Patients (pts) with stage I-IIA supra-diaphragmatic non-bulky disease (mediastinal mass ratio <1/3 and no disease >10 cm) were eligible. Stanford V-C (cyclophosphamide substituted for nitrogen mustard of Stanford V) was administered x 8 weeks (total doxorubicin 75 mg/m^2 and bleomycin 20 mg/m^2). G-CSF was permitted for grade (gr) ≥3 neutropenia. Two weeks after completion of CT pts received INRT (20 Gy) including initially involved nodes with 1-1.5 cm margins axially and 2-5 cm cephalo-caudad. All pts were treated and followed at Stanford. Endpoints were toxicity and efficacy [progression free survival (PFS) and overall survival (OS)].

Results: 43 pts were accrued with a median age of 31 years (range19-66); 16% had stage I and 84% stage II disease. Twenty pts (47%) were considered ''unfavorable'' according to German Hodgkin Study Group (GHSG) criteria; >2 nodal sites (n=20) or elevated ESR (≥ 50 mm/hr) (n=3). G-CSF was required in 60% of pts due to gr 3 (n=10) or 4 (n=16) neutropenia. Other gr 3 toxicities included: fever (n=1), pain (n=3), acute pulmonary embolism (n=1) and epigastric pain (n=2). At a median follow-up of 4.8 years (range 0.8-9.6), the overall PFS and OS are 94.6% and 100% respectively. For pts with unfavorable risk factors the PFS and OS are 88.5% and 100% respectively. Therapy failed in 2 pts both considered ''unfavorable'' per GHSG criteria with >2 nodal sites. The mean time to relapse was 23 months (range 16-30). One pt failed within the RT field and the second infield and distant. Both were salvaged successfully with secondary therapy, and stem cell support. No bleomycin lung toxicity or radiation pneumonitis have been noted and to date there have been no second malignancies, secondary leukemia, or cardiac events.

Conclusions: The G5 regimen (8 wks Stanford V-C and 20 Gy INRT) has excellent results with minimal toxicity in pts with non-bulky stage I-II HL including those defined as ''unfavorable'' by the GHSG criteria. The outcome is comparable to studies using more intense CT and IFRT. Longer follow up is required to assess the impact of this reduced intensity approach on CT and RT related late effects.

284 EVALUATION OF THE NORDIC STUDY FOR EARLY STAGE HODGKIN LYMPHOMA

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Introduction/Background: Between 1999 and 2005 patients with early stage HL, 18-70 years of age, in the Nordic countries were treated according to a protocol with less extensive treatment than earlier.

Patients and Methods: The design of the study was prospective and population based. Patients without risk factors (RF) were treated with two ABVD followed by 30 Gy IFRT (if bulky disease 35 Gy). Those with RF were given four ABVD before RT. Initially some patients received MOPP/ABV. Primary endpoints were disease-free survival (DFS), over-all survival (OS) and late side effects. Only patients with classical HL were evaluated.

Results: 434 patients from Sweden (n=256) and Norway (n=178) were evaluated. Median follow up is 65 months (range 2-127). 118 patients were in stage IA and 316 in stage IIA. RF were present in 191 cases. Mean age was 37.2 years. The histology was NSHL in 300 cases, MCHL in 84, 32 LRCHL, 1 LD and 16 not classifiable. After treatment 290 (66.6%) were in CR, 143 (32.8%) in CR(u) and2 (0.5%) patients had progressive disease. OS and DFS at 5-years was 96.1% and 92%. DFS at 10 years was 88.9%. Relapse occurred in 35 cases (8%). Salvage treatment was high-dose CT followed by autologous stem-cell transplantation (SCT) in 18 cases (51%). Conventional chemotherapy was given in 11 cases and RT in 10 cases. New CR was achieved in 24 cases (68.5%), 5 were still under treatment and in 3 cases no new CR was

achieved. Eight patients suffered a second relapse. Two of those had a new CR, 4 no new CR, and 2 were still under treatment. From 20 deceased patients 7 died from HL and 2 with HL. Out of the 11 who died without HL the cause was NHL in 6 cases. Patients who had a recurrence tended to have a slower response of the primary treatment with a CR after 2 and 4 courses in 7% vs 19% and 6% vs 23% p=0.0748. The greatest difference between the groups was found at the final evaluation where significantly fewer in the group with relapse had achieved CR (41% vs 67% p= 0.0035).

Conclusions: OS and DFS seems to be comparable to older protocols and to similar treatment in controlled studies. It is too early to evaluate late side-effects. Of all the variables, it was only the outcome of treatment that significantly affected the relapse rate, although the evaluation after two courses also showed a trend towards better DFS in patients with CR. This is well corresponding with FDG-PET studies that show a clear correlation between early response and final outcome.

285 DOSE-ESCALATION WITH BEACOPP ESCALATED IS SUPERIOR TO ABVD IN THE COMBINED-MODALITY TREATMENT OF EARLY UNFAVORABLE HODGKIN LYMPHOMA (HL): FINAL ANALYSIS OF THE GERMAN HODGKIN STUDY GROUP (GHSG) HD14 TRIAL

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Background/Aim: 4xchemotherapy plus involved-field radiotherapy (IFRT) is standard of care for early unfavorable HL. In our previous HD8 study, freedom from treatment failure (FFTF) at 5 years in this patient cohort was 83%. The rationale for HD14 was to improve this result by increasing dose intensity using $BEACOPP_{esc}$.

Methods: Between January 2003 and July 2008, 1655 patients between 16 and 60 years with histologically confirmed diagnosis of HL were randomized to either 4x ABVD (arm A) or 2x $BEACOPP_{esc}$ followed by 2x ABVD (arm B, "2+2"). Patients had to have CS I, IIA with one of the following risk factors: large mediastinal mass (a), extranodal disease (b), elevated ESR (c), or ≥ 3 nodal areas (d), IIB with risk factors c or d. All patients received 30Gy IFRT. Primary objective was the improvement of FFTF.

Results: 1623 patients were documented and are evaluable (A=818, B=805). Patient characteristics were well balanced. The overall response rate was 95% in each arm. The estimated 4-year FFTF rate was 89.3% in arm A and 94.7% in arm B (p=0,0001, HR=2.04, 95%-CI: 1.39-2.94). Progressive disease was 2.9% versus 0.9% (A versus B); early relapse rate 2.8% versus 0.9%, late relapse rate 2.3% versus 0.9%. Acute grade III-IV toxicity rates were higher in arm B (87.1%) than in arm A (50.7%). However, we observed no differences in overall survival, treatment-related death or secondary neoplasia rates.

Conclusion: Intensifying treatment for patients with early unfavorable HL using $BEACOPP_{esc}$ in the "2+2" design has significantly improved the outcome as compared to 4x ABVD, both followed by IFRT. Thus, "2+2" is the new standard of care for early unfavorable HL.

286 A PHASE I STUDY TO INVESTIGATE DOSE ESCALATION OF DOXORUBICIN IN CYCLES 1-3 OF ABVD CHEMOTHERAPY FOR HODGKIN LYMPHOMA AND TO CORRELATE THIS WITH BLOOD-BORNE BIOMARKERS OF TUMOUR RESPONSE AND TOXICITY

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The GHSG has shown that chemotherapy induced grade III/IV leukopenia correlates strongly with improved treatment response suggesting that BSA dosing produces variable biological effects. This may explain differences in toxicity, response, PFS and OS, and argues for a more rational approach to dosing. We report interim data from a phase 1 dose escalation cohort study aimed at identifying the maximum tolerated dose (MTD) of doxorubicin within cycles 1-3 ABVDand the role of circulating biomarkers for PD-driven dosing.

Dose escalation was performed on a cohort basis (1: 35 mg/m^2; 2: 45 mg/m^2; 3: 55 mg/m^2; 4: 65 mg/m^2) with doxorubicin omitted from later cycles to maintain a cumulative dose of 103%-130% despite maximal dose intensity of 260% in cycles 1-3. Subjects received PEG-filgrastim after every doxorubicin dose. BVD was given at standard doses.

Dose limiting toxicity (DLT) was defined as grade 4 haematological toxicity lasting ≥5 days, or grade 3 non-haematological (excepting nausea, vomiting) at any time during treatment. MTD was defined as the cohort below which ≥3 subjects experienced DLT. At MTD 6 more patients were recruited to expand this cohort to 12. Blood-borne nucleosomal DNA based markers of cell death and CK18 based biomarkers of toxicitywere collected on days 1,3,8,15,17, 22 of each escalated cycle. Relevant ELISAs are being run to GCLP standards and results correlated with outcomes. 24 subjects (13 females; median age 34) were recruited. DLT was reached in cohort 3: 1 subject experienced G3 neuropathy and G3 bleomycin lung toxicity, another G3 palmar-plantar erythema and a third G3 PPE, G3 neuropathy and G3 neutropaenic infection. All DLTs occurred within the first 3 dose-escalated cycles. Haematological toxicity was manageable with 9 G3/4 events in cohort 2 and 4 in cohort 3. With 23/24 so far evaluable, PET-CT responses are: CR 17, PR 5, PD 1.

These data suggest that ABVD may be delivered safely with PEG-filgrastim support at a doxorubicin dose of 45 mg m^{-2} in cycles 1-3. Response rates are comparable with published data. Analysis of secondary endpoints and correlation with blood-borne biomarkers will be presented, and future plans to develop PD driven dosing to overcome BSA limitations discussed.

287 COMPARATIVE CLINICAL RESPONSES OF THREE CHEMOTHERAPY SCHEDULES (VEPEMB, ABVD, CLVPP) IN 175 HODGKIN LYMPHOMA PATIENTS OVER 60YS EVALUATED AS PART OF THE SHIELD (HODGKIN ELDERLY) STUDY.

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Introduction: Outcome in Hodgkin lymphoma (HL) patients >60ys is unsatisfactory. The SHIELD Study is the largest prospective study in this group. 175 UK patients were studied from 2004-2009.

Methods and Results: The majority (N=103); median age 72.3ys, 32(31%) early stage (ES), 71(69%) advanced stage (AS), entered a phase 2 study using the VEPEMB schedule (3 courses + radiotherapy (RT) for ES disease, 6 courses for AS). 82% of ES patients receiving at least 2 courses attained CR/CRu (intention to treat 72%). 71% of AS patients receiving at least two treatments attained CR/CRu (intention to treat 61%). All patients treated with VEPEMB had WHO grade 3/4 haematological toxicity unless prophylactic GCSF was used, minor therapy delay occurred in all patients. Major dose reduction occurred in 26% of patients. There were 3 (3%) septic deaths. 7 patients died in CR, 4 of other cancers (1 AML), 3 of vascular events. 84% of patients entering CR remain in remission at median of 3ys.

The most frequent alternative therapy was ABVD (N= 35); median age 65.8ys, 13(36%) ES (2-3 courses +RT), 22 (64%) AS (6 courses). 68% of ES patients attained CR/CRu, 32% PR, with no septic deaths. 10/22 (45%) of patients with AS disease attained CR/CRu, 18% PR, 18% NR. Septic deaths occurred in 4/22 AS patients. Overall septic death rate for ABVD was 11%. The ABVD group were more favourable in terms of age and ECOG status.

Of 19 patients given CLVPP therapy, 18 had >2 treatment courses. 3/15 AS patients (20%) obtained CR, 2/4 ES patients obtained CR. All 13 patients designated ''frail'' on the SNLG/ACE-27 co morbidity scale died within 6 months. None attained CR and only 1 achieved PR. This modified ACE-27 assessment tool was a powerful negative indicator of survival.18 patients received RT alone, palliative care or other chemotherapy.

Review histology of VEPEMB patients was MC-31, NS-45, cHL-NFC-23, HL undiff-4. Clonal EBV expression in RS cells assessed in 85 patients, 49% EBV+ve. CR rates in EBV+ve and EBV-ve were identical (77%v76%). EBV status and survival awaits further follow up.

Conclusion: The results indicate that ABVD did not perform as well as VEPEMB, remission rates were lower in ES and AS patients for ABVD andtreatment-related septic death (11%v3% p<0.05) was higher. With VEPEMB if >2 treatments are completed then outcome in ES disease is excellent with only 2 relapses, median follow up of 3ys. Similarly, 70% AS patients receiving >2 courses achieved CR and remissions were sustained at median of 3ys with one relapse.

288 UPDATED RESULTS OF A PHASE II TRIAL OF BENDAMUSTINE IN RELAPSED AND REFRACTORY HODGKIN LYMPHOMA

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Introduction: We previously reported the interim results of our phase II study of bendamustine in relapsed and refractory (rel/ref) Hodgkin lymphoma (HL). This represents our updated analysis. No standard treatment exists for rel/ref HL following

autologous stem cell transplant (ASCT) failure and prognosis is poor. Reduced intensity allogeneic stem cell transplant (alloSCT) offers a chance of cure in a subset of patients; therefore the goal of treatment should be to reduce disease burden to facilitate alloSCT. We sought to evaluate the efficacy of bendamustine in rel/ref HL and its role as a bridge to alloSCT following ASCT failure.

Methods: Our primary outcomes were response rate and, for eligible patients, referral to alloSCT. Patients received bendamustine 120mg/m2, for two consecutive days, every 28 days. Pegfilgrastim was administered with each cycle and treatment was delayed until absolute neutrophil count was > 1000/ul and the platelet count was > 75,000/ul. Dose was reduced to 100mg/m2 in cases of treatment delays > 5 days due to neutropenia or thrombocytopenia or for grade 3 non-hematologic toxicities. Patients were evaluated for response after 2, 4, and 6 cycles using Cheson 2007 criteria. Patients deemed eligible for alloSCT were referred when they had maximal response to bendamustine; otherwise, patients received a maximum of 6 cycles.

Results: To date, 36 patients enrolled. Median age was 34 (range 21-75) and 23 (64%) were females. Seven (19%) had B symptoms and 4 (11%) had bone marrow involvement. Median previous treatments were 4 (range 1-17). Twenty-seven patients previously failed ASCT, 6 failed alloSCT. The most common adverse reaction was thrombocytopenia affecting 16 (46%) patients, with 5 (14%) patients experiencing grade 3 or 4. Of 117 treatment cycles, 12 (10%) were delayed due to thrombocytopenia (8), neutropenia and pneumonia (1), pneumonia (1), HSV encephalitis (1), and an upper respiratory infection (1). Three patients were withdrawn after cycle 1 (2) and cycle 2 (1) due to prolonged thrombocytopenia. Thirty-three patients are evaluable for response. There were 11 CRs (33%), 8 PRs (24%), 2 SD (6%); ORR was 57%. Mean response duration was 5.7 months (range 1.5-7.9 months). Of 22 patients initially deemed eligible for alloSCT, 5 ultimately went on to alloSCT after bendamustine. The most common reason for failure to achieve alloSCT was progression of disease.

Conclusion: Bendamustine is well tolerated and active in this heavily pre-treated patient population. Future studies will combine bendamustine with novel agents in rel/ref HL.

289 EVEROLIMUS PLUS SORAFINIB FOR THE TREATMENT OF HODGKIN LYMPHOMA

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mTOR inhibition appears to hold promise in the treatment of lymphoid malignancies. We have previously noted a 47% response rate in patients with relapsed/refractory Hodgkin lymphoma when treated with Everolimus at 10 mg by mouth daily. In the current study, we have enrolled 17 patients with relapsed/ refractory Hodgkin lymphoma in a phase Ib/II clinical trial of Everolimus and Sorafenib. Baseline characteristics included 11 female/ 8 male; median age 32 (range 22-60); median number of prior therapies 4, all patients had undergone prior autologous stem cell transplantation, one patient had undergone prior allogeneic transplantation; 2 patients had undergone prior mTOR therapy. 8 patients were enrolled in the phase Ib portion of the clinical trial with escalating doses of Everolimus and Sorafenib; 9 patients have been enrolled in the phase II portion with Everolimus given at 5 mg by mouth daily and Sorafenib at 200 mg by mouth twice daily. Overall response rate of 59% with 2 CR/ 9PR. 6 patients had stable disease as best response; 2 patients had progressive disease at first response assessment. Median duration on study medication was 12 months. Two patients went off study due to adverse events. Toxicity was similar to that seen with Everolimus alone, with the exception of increased skin toxicity in this study. 12 patients have discontinued study, with 5 patients remaining on study at 36, 29, 21, 18 and 9 months. Although this represents a small number of patients, it has confirmed the activity of mTOR inhibition in patients with Hodgkin lymphoma and suggests a higer response rate with the addition of Sorafenib.

290 BLEOMYCIN-INDUCED PULMONARY FIBROSIS (BPF) IN HODGKIN LYMPHOMA (HL) PATIENTS: IS GRANOLOCYTE-COLONY STIMULATING FACTOR (G-CSF) A RISK FACTOR?

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Introduction: BPF is a significant clinical problem in the management of patients with Hodgkin lymphoma. G-CSF has been proposed as a possible risk factor for bleomycin-induced lung fibrosis in animal models. Human data on this issue are still lacking.

Material: Results from newly diagnosed HL patients seen at our department in the period 2006-2010 were analysed. Pre-therapeutic parameters such as age, cumulative bleomycin dose, renal function, pre-existing pulmonary disease, use or not of G-CSF were recorded. The correlation of these parameters to subsequent development of BPF was evaluated.

Results: A total of 105 HL patients were included in this analysis. All patients received ABVD or ABVD/COPP. Eleven patients developed bleomycin-induced pneumonitis and subsequent lung fibrosis (10.4%). They had all received G-CSF: Pegfilgrastim (6 pt) / Pegfilgrastim and Filgrastim (4 pt), Filgrastim (1 pt). None of the patients that had not received G-CSF developed BPF. Although only a trend not reaching statistical significance (p=0.07), due to the limited number of patients in the non-G-CSF group, it was noteworthy that none of the patients in this latter group developed BPF. No significant difference in age (p=0.098) or cumulative bleomycin dose was found between the two groups (p=0.69).

	BPF Yes	No	N Total
+ G-CSF	11 (10.4%)	72 (68.6%)	83 (79.0%)
- G-CSF	0 (0.0%)	22 (21.0%)	22 (21.0%)
N Total	11 (10.4%)	94 (89.6%)	105

Pearson chi2, p=0.07

Conclusions: All cases with BPF found in this series were in the GCS-F treated group. Although only representing a trend due to the small size of the non-GCSF treated group, this observation calls for further investigation on an extended cohort. Additional risk factor analysis, e.g. smoking habits, occupational exposures, BPF associated gene expression, are currently been analysed.

291 NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA BEHAVES AS A DISTINCT CLINICAL ENTITY WITH GOOD OUTCOME: EVIDENCE FROM 14 YEAR FOLLOW-UP FROM THE WEST OF SCOTLAND CANCER NETWORK

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Introduction: Clinically and biologically, nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) has much more in common with germinal-centre derived B-cell non-Hodgkin lymphomas (NHL) than classical Hodgkin lymphoma. Management of NLPHL remains controversial. Here we present data from a large case series derived from 14 years of experience in the West of Scotland.

Materials and methods: Cases were identified through the WoSCAN lymphoma database (01/01/97 – 31/10/10). Patients were managed by 46 haemato-oncologists throughout the region (population 2.6M). Data were obtained by direct case note review and analysed using SPSS 15.0.

Results: Seventy cases were identified; median follow-up was 50 months (range 11-165). Median age was 38.5 yrs (range 11-79) and 70% were male. B symptoms were present in 6% of patients. No stage I/II patients had risk factors as defined by the EORTC. 72% of patients had supra-diaphragmatic disease and only 21% of patients had axial disease.

First-line treatment

Stage	(%)	Observation	Radiotherapy	Chemotherapy	Combined Modality
I	50	2	26	1	6
II	30	2	11	3	5
III	11.4	0	0	8	0
IV	8.6	0	0	4	2

The most frequent chemotherapeutic regimen employed was ABVD. The mean radiotherapy dose was 30.0Gy (range 20-40Gy.) Of the four patients managed by observation, one developed a transformation to DLBCL at 16 months. The other three continue to have stable disease at a median of 57 months from diagnosis. 8.6% of NLPHL patients relapsed at a mean of 53 months (range 13-121). The majority of these were treated with chemotherapy, including one patient who received an autologous PBSCT. 5.7% of patients had or developed high-grade transformation to DLBCL and all were treated with R CHOP with one patient proceeding to autologous PBSCT. All relapses and transformations were salvageable. There were two deaths, neither of which was related to NLPHL. The 5 yr relapse-free survival was 73%, transformation-free survival 91% and overall survival 100%.

Conclusions: In our large, multi-centre series, NLPHL behaves as a distinct clinical entity, often presenting at early stage with localised peripheral lymphadenopathy and without B symptoms. It has an excellent outcome. Although late relapses and transformation were seen, all were salvageable. It may be possible to reduce intensity of therapy in NLPHL without affecting OS, with the aim of reducing toxicity and late effects of therapy.

292 PROSPECTIVE EVALUATION OF FATIGUE IN HODGKIN LYMPHOMA PATIENTS: A GERMAN HODGKIN STUDY GROUP REPORT

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Background: Recently fatigue (FA) has emerged as a major subject in the evaluation of Quality of life (QoL). Up to now there is no comprehensive data on the longitudinal development of FA, risk factors, correlations to other QoL scales and the impact on overall survival (OS). Thus, the German Hodgkin Study Group analyzed patients of the prospectively randomized HD 10-12 trials.

Methods: QoL and FA were assessed with a psychometrically proven questionnaire (QLQS) which contains the EORTC QLQ-C30 and the MFI20 among other scales and items. Patients answered the QLQS before, during, and after end of therapy as well as in predetermined follow-ups. For all functional scales (FS) and FA, longitudinal courses up to 27 months from diagnosis are described. Reference values from a German control population (GCR) were used for interpretation. The predictive value of FA at baseline for overall survival (OS) was tested in Cox proportional hazards analyses together with other known risk factors.

Results: Of 4,160 patients included in HD10-12, 3,208 were evaluable for this analysis. Before therapy, patients had clearly poorer mean scores for FA and the FS in comparison to the GCR which increased with stage. FA showed a further deterioration under therapy. In the follow up we observed generally improvements compared to baseline, but FA did not recover to GCR values. Interestingly, no relevant effect of therapy intensity or type was seen. FA correlated highest with physical and role functioning scales. Severe FA (sFA, value ≥50 on a relative scale from 0-100) was found permanently in 6% of patients, 6.8% newly developed long term sFA but had normal baseline values. In 44.7% of patients sFA was never observed, 17.4% had sFA only during treatment, and 15.1% had sFA at baseline which vanished after therapy. SFA at baseline was mainly influenced by stage, tumor mass indices and to a lesser extent by gender. SFA at baseline and at 1 year remained as significant predictor for long term FA. In addition, sFA at baseline is a significant, strong and independent risk factor for death from any cause ($p<.05$, HR= 1.5)

Conclusion: This first longitudinal analysis on FA in all HL-stages shows lymphoma associated FA before therapy, and an improvement over time but no recovery to GCR values in the follow-up. Importantly there seems to be no effect of therapy intensity or type on long term FA. Additionally, baseline sFA is a strong, independent risk factor for OS and should be assessed in HL patients. Best predictor for long term FA is sFA at 1 year. Based on these data further interventional studies will be planned.

293 LONG-TERM RISK OF CARDIAC AND VALVULAR DISEASE AFTER INVOLVED NODE RADIOTHERAPY AND MANTLE FIELD FOR HODGKIN LYMPHOMA

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Background: The risk of developing cardiac disease (CD) for long-term Hodgkin lymphoma (HL) survivors after mediastinal radiotherapy (RT) is under debate, as current data are, primarily, derived from patients treated with the outdated Mantle Field (MF) technique. In this work, we compare doses to the heart and four heart valves with Involved Node RT (INRT), the present standard of treatment, and MF. We also derive and compare the excess absolute risk (EAR) of developing CD using both techniques.

Materials and Methods: We included all adolescents-young adults with supradiaphragmatic, clinical stage I-II HL treated at our institution 2006-2010 (29 patients). All patients were treated with chemotherapy and INRT (30-36 Gy). We then simulated a MF plan for each patient, delivering 36 Gy. We derived a logistic dose-response curve for the 25 year risk of any CD and valvular disease (VD) using published data from a HL material [1]. For each patient we estimated the risk of any CD and VD from the individual dose volume histogram and the dose-response function.

Results: The calculated mean doses to the heart and four valves with INRT and MF treatment and the corresponding EAR are presented in Table 1.

	Mean dose, Gy (range)		Mean EAR, % (range)	
	INRT	MF	INRT	MF
Heart	8.7 (0-28.6)	27.5 (23-33.9)	1.8 (0.4-9.9)	9.1 (5.5-16.6)
Aortic valve	18.1 (0-34.2)	35.7 (33-40.4)	0.6 (0-4.2)	9.2 (2.5-30.3)
Pulmonic valve	19.8 (0-36.5)	37.2 (33.7-41.6)	0.2 (0-1.3)	1.9 (0.4-4.5)
Mitral valve	8.9 (0-36.4)	34.4 (32.3-36.8)	0.2 (0-5.7)	3.1 (1.1-6.7)
Tricuspid valve	8.3 (0-37.8)	35.4 (32.2-41)	0.1 (0-3.9)	2.2 (0.4-8.4)
Any valve			1.2 (0-10.7)	16.4 (4.7-49.8)

Table 1. Mean dose and mean EAR of all 29 patients with INRT and MF.

Conclusions: Our results show, that the mean dose to the heart and four heart valves was much lower with the INRT plan compared to the MF plan for most patients. However, for a subset of patients, even INRT plans will expose the heart and heart valves to high doses with a 25 year excess risk of a cardiac event of up to 9.9%. For such patients the use of even more conformal techniques than INRT and/or further dose reduction is needed to minimize the risk of severe long-term complications.

References

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294 INCREASED RISK OF COLORECTAL CANCER IN PATIENTS TREATED FOR HODGKIN LYMPHOMA: A LONG-TERM FOLLOW-UP STUDY IN THE NETHERLANDS

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Background: After the introduction of modern radiotherapy (RT) and combination chemotherapy (CT), Hodgkin lymphoma (HL) has become the prototype of a curable malignancy. However, it has been demonstrated that RT and CT can increase the risk of various second malignancies. Data on colorectal cancer (CRC) risk are scarce. Our study aims to quantify CRC risk following HL treatment in a Dutch cohort by age at diagnosis, follow-up duration, treatment and attained age.

Material and methods: Over the past decades we identified a large cohort of 2514 5-year HL survivors, diagnosed before age 51 and treated between 1965 and 1995. Treatment consisted of RT (30%), CT (10%) or CT+RT (60%). CT usually consisted of MOPP or MOPP/ABV(D). Median follow-up was 17.8 years.

Results: Preliminary results show that HL patients have a 3.8-fold (95% confidence interval (CI) 2.7-5.1) increased standardized incidence ratio (SIR) of developing CRC compared to the general population, with an absolute excess risk of 8.1 per 10,000 patients/year. Thirty-eight CRC patients were identified (21 colon, 17 rectum). The highest SIR (7.5, 95% CI 3.4-14.3) was seen for patients treated before age 25. Cumulative incidence was 1.9% (95% CI 1.3-2.7) at 30 years of follow-up. Especially for colon cancer, the SIR increased with longer follow-up duration (9.3, 95% CI 3.4-20.2 in 30-year survivors). No increased SIR for CRC was found in patients treated with RT alone. Significantly increased SIRs were found in patients treated with CT+/-supradiaphragmatic RT (3.8, 95% CI 2.2-6.1) and with CT+infradiaphragmatic RT (6.9, 95% CI 4.0-11.2). The hazard ratio of CT was 2.24 (95% CI 1.03-4.85). Results show that a 40-year old HL survivor treated before age 25 has the same CRC risk as a 55-60-year old person from the general population. More data will be available in June 2011.

Conclusion: We showed in a population of HL patients treated between 1965 and 1995, that long-term survivors have a slightly increased risk of developing CRC, especially when treated with chemotherapy and infradiaphragmatic radiotherapy; following radiotherapy only no increased risks were observed.