Hodgkin lymphoma

282  NODULAR SCLEROSIS-TYPE CLASSICAL Hodgkin lymphoma in the elderly: Poor prognosis and heterogeneous nature


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%) than NSCHL-y. The prognosis of NSCHL-e was poorer than that of NSCHL-y (P < 0.001). But when CD20-positive and granzyme B-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 typical of CHL. Some of NSCHL-e cases had atypical phenotypic HRS cells, namely CD20-negative, granzyme B-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 and T-cell lymphomas. 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).

<table>
<thead>
<tr>
<th>NSCHL-e (n=84)</th>
<th>NSCHL-y (n=237)</th>
<th>P  §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>63/21</td>
<td>116/121</td>
</tr>
<tr>
<td>Age(y), median (range)</td>
<td>65 (50-86)</td>
<td>27 (19-49)</td>
</tr>
<tr>
<td>PS &gt;1</td>
<td>10 (18%)</td>
<td>19 (12%)</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>41 (53%)</td>
<td>70 (32%)</td>
</tr>
<tr>
<td>B symptoms</td>
<td>32 (41%)</td>
<td>74 (34%)</td>
</tr>
<tr>
<td>Extranodal &gt;1site</td>
<td>6 (8%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>BM involvement</td>
<td>4 (5%)</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>LDH &gt;normal</td>
<td>40 (63%)</td>
<td>94 (53%)</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD20</td>
<td>3/56 (8%)</td>
<td>4/79 (5%)</td>
</tr>
<tr>
<td>CD15</td>
<td>50/78 (64%)</td>
<td>145/219 (66%)</td>
</tr>
<tr>
<td>CD30</td>
<td>73/79 (92%)</td>
<td>208/219 (95%)</td>
</tr>
<tr>
<td>CD20</td>
<td>13/54 (24%)</td>
<td>12/155 (8%)</td>
</tr>
<tr>
<td>EBV</td>
<td>29/75 (39%)</td>
<td>14/207 (7%)</td>
</tr>
<tr>
<td>Granyme B</td>
<td>8/57 (14%)</td>
<td>5/142 (4%)</td>
</tr>
</tbody>
</table>

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.

283  ABBREVIATED 8 WK CHEMOTHERAPY (CT) + INVOLVED NODE RADIOTHERAPY (IRRT) 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 +50 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 × 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 for 8 weeks (total doxorubicin 75 mg/m² and bleomycin 20 mg/m²). G-CSF was permitted for grade (gr) ≥3 neutropenia. Two weeks after completion of CT pts received INRT (20 Gy) including involved nodes with 1-1.5 cm margins axially and 2-5 cm cephalo-caudally. 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 (range 19-66); 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 66% 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 epigastriac 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 field and the second infield and distant. Both were salvaged successfully with secondary therapy, and stem cell support. No blomycin 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 IRRT. 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 was 65 months (range 2-127). 118 patients were in stage IIA 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 (a) and 2 (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 (53%). 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 3 with HL. Out of 1 who did not die an NHL was 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 UNFAVOURABLE HODGKIN LYMPHOMA (HL): FINAL ANALYSIS OF THE GERMAN Hodgkin STUDY GROUP (GHSG) HD14 TRIAL

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Dose escalation was performed on a cohort basis (1: 35 mg/m²; 2: 45 mg/m²; 3: 55 mg/m²; 4: 65 mg/m²) with doxorubicin omitted from later cycles to maintain a cumulative doxorubicin dose of 1150-1300 despite maximal dose intensity of 2600 in cycles 1-3. Subjects received PEG-filgratim after every doxorubicin dose. BVD was given at standard doses.

Dose limiting toxicity (DLT) was defined as grade 4 haematological toxicity lasting 65 days, or grade 3 non-haematological (excepting nausea, vomiting) at any time during treatment. MTD was defined as the highest dose level at which 3 subjects experienced DLT. At MTD 6 were patients were recruited to expand this cohort to 12. Blood-borne nucleosomal DNA based markers of cell death and CK18 based biomarkers of toxicity were collected on days 1,3,8,15,17, 22 of each escalated cycle. Relevant ELISAs and the EORTC quality of life questionnaire were collected. 18 patients received RT alone, palliative care or other alternative therapy (N= 35); median age 65.8ys, 13(36%) ES (2-3 courses +2), 22 (64%) CHV (6 doses). 68% of ES patients attained CR/Cr (13% CR, 32% PR, with no septic death, 10/22 (45%) of patients with AS disease attained CR/Cr, 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. The most frequent alternative therapy was ABVD (N= 35); median age 65.8ys, 13(36%) ES (2-3 courses +2), 22 (64%) CHV (6 doses). 68% of ES patients attained CR/Cr (13% CR, 32% PR, with no septic death, 10/22 (45%) of patients with AS disease attained CR/Cr, 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.

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/Cr (intention to treat 72%). 71% of AS patients receiving at least two treatments attained CR/Cr (intention to treat 61%). All patients treated with VEPEMB had WHO grade 3/4 haematological toxicity unless prophylactic GCFS was used, minor therapy delay occurred in all patients. Major dose reductions occurred in 26% of patients. 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.

Conclusions: Intensifying treatment for patients with early unfavorable HL using BEACOPP esc. in the “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 leuokopenia 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 I dose escalation cohort study aimed at identifying the maximum tolerated dose (MTD) of doxorubicin within cycles 1-3 ABVD and the role of circulating biomarkers for PD-driven dosing.

The most frequent alternative therapy was ABVD (N= 35); median age 65.8ys, 13(36%) ES (2-3 courses +2), 22 (64%) CHV (6 doses). 68% of ES patients attained CR/Cr (13% CR, 32% PR, with no septic death, 10/22 (45%) of patients with AS disease attained CR/Cr, 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.

Conclusion: The results indicate that ABVD did not perform as well as VEPEMB, remission rates were lower in ES and ES patients for ABVD andtrtment-related septic death (11/6% vs 0/05% 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 (ref/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 daily intravenous infusions of the drug was administered with each cycle of treatment was delayed until absolute neutrophil count was > 1000/µl and the platelet count was > 75,000/µl. Dose was reduced to 100mg/m² in cases of treatment delays > 5 days due to neutropenia or thrombocytopenia or for grade 3 non-hematologic toxicity. 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 toxicity. 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 an attempt to further improve outcomes in patients with rel/ref HL.

289 EVEROLIMUS PLUS SORAFINIB FOR THE TREATMENT OF REL/REF HL

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HODGKIN LYMPHOMA

290 BLEOMYCIN-INDUCED PULMONARY FIBROSIS (BPF) IN Hodgkin lymphoma (HL) PATIENTS: IS GRANOCYTE-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 of bleomycin, and use 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 pts) / Filgrastim (4 pts). 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=0.998) or cumulative bleomycin dose was found between the two groups (p=0.69).

Pearson chi2, p=0.07

Conclusions: All cases with BPF found in this series were in the G-CSF-treated group. Although only representing a trend due to the small size of the non-G-CSF 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 being analysed.
**292 PROSPECTIVE EVALUATION OF FATIGUE IN HODGKIN LYMPHOMA PATIENTS: A GERMAN HODGKIN STUDY GROUP REPORT**

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**Methods:**

Quality of life (QoL) and fatigue (FA) were assessed with a psychometrically proven questionnaire 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. Up to now there is no comprehensive data on the longitudinal therapy intensity or type was seen. FA correlated highest with physical and role functioning scales. Severe FA (≥80 on a relative scale from 0-100) was found permanently in 6% of patients, 6.8% newly developed long term FA but had normal baseline values. In 44.7% of patients FA was never observed, 17.4% had FA only during treatment, and 15.1% had FA 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, FA at baseline is a significant, strong and independent risk factor for death control under therapy. In the follow up we observed generally improvements compared to comparison to the GCR which increased with stage. FA showed a further deterioration of 4,160 patients included in HD10-12. FA was correlated highest with physical and role functioning scales. Severe FA (≥80 on a relative scale from 0-100) was found permanently in 6% of patients, 6.8% newly developed long term FA but had normal baseline values. In 44.7% of patients FA was never observed, 17.4% had FA only during treatment, and 15.1% had FA 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, FA at baseline is a significant, strong and independent risk factor for death control under therapy. In the follow up we observed generally improvements compared to comparison to the GCR which increased with stage. FA showed a further deterioration.

**Conclusion:**

This longitudinal analysis on FA in all HL-stages shows lymphoma associated baseline 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 death control under therapy. In the follow up we observed generally improvements compared to comparison to the GCR which increased with stage. FA showed a further deterioration.

**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 CT (30%), CT+RT (60%), CT treated with RT alone. For each patient treated with CT 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.