5. Hodgkin’s Disease

**COMPOSITE HODGKIN’S DISEASE AND TRANSFORMED LYMPHOMA: EVIDENCE FOR ORIGIN FROM A SINGLE CLONE WITH DIVERGENT MECHANISMS OF TUMOR PROGRESSION**

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Molecular and immunohistochemical analyses were performed on frozen and paraffin-embedded tissues from a patient with an unusual lymphoproliferative malignancy characterized by the presence of low grade small cleaved cell lymphoma (LGL) in bone marrow (BM), and composite Hodgkin’s disease (HD) and high grade small non-cleaved cell lymphoma (HGL) within separate areas of a single lymph node (LN). PCR analysis of DNA extracted from each of three sites revealed evidence of (14;18) translocation involving bcl-2 rearrangement at the major breakpoint region (MBR). DNA sequencing of the two separate PCR-amplified products from the LN tissue that contained HD and HGL showed evidence of two different bcl-2 rearrangements which share MBR breakpoints at the same nucleotide on chromosome 18 and identical N-insertions but which differ by a deletional mutation. This finding is consistent with the presence of two distinct but related clonal populations. Reed-Sternberg cells from the HD component of the LN tissue showed reactivity with antibodies directed against CD30 (Ki-13), CD15 (Leu-M1), bcl-2 protein and EBV latent membrane protein (EBV-LMP) but not for CD20 (L26). In contrast, the HGL cells stained with antibodies directed against CD20 and bcl-2 protein and not with CD30, CD15 or EBV-LMP, findings shared with the LGL cells in BM, and did not exhibit EBV or HD markers. Additionally, p53 expression was detected in the HD and HGL tissues but not in the LGL cells. Our findings suggest that 1) the composite HD and HGL originated from a single clone and 2) the acquisition of EBV infection and p53 expression are associated with the development of HD in this patient.

**HODGKIN’S DISEASE IMMUNOHISTOPATHOLOGY AND THERAPEUTIC OUTCOME (1980-1995)**

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Introduction: Hodgkin’s disease (HD) was thought to be common among the Middle Eastern population. The population of the United Arab Emirates (UAE) is estimated to be 900,000 nationals and 1.4 million expatriates, most of whom are from the Middle East and Indian subcontinent. The Medical Faculty is located in Al Ain where Tawam Hospital is the oncology referral center for the UAE.

Patient, material and methods: One hundred and seventy-three patients with HD were diagnosed between 1980 and 1995 in Al Ain. The histological diagnosis of HD was based on the presence of Reed-Sternberg (R-S) cells in a reactive inflammatory milieu. Immunohistochemistry with CD30 (Ki-1 Ag, Ber-H2) was utilized for confirming presence of R-S cells. Other B-cell and T-cell antibodies were utilized to confirm the heterogeneity of the inflammatory background, MOPP chemotherapy, radiotherapy, or combined chemotherapeutic regimens. The Medical Faculty is located in Al Ain where Tawam Hospital is the oncology referral center for the UAE.

Results: Most of the patients were males (130 males and 43 females), ranging in age between 4 and 81 years (average 27 years). Of 173 patients with HD, 58 had nodular sclerosis (NS), 49 had mixed cellularity (MC), 32 had lymphocytic predominance (LP), and 21 had lymphocytic depleted (LD) subtypes. In 13 patients, the subtype could not be determined. Of the 94 HD patients, who presented between 1980 and 1995, 30 patients had stage I, 16 patients had stage II (25 patients had stage III, 23 patients had stage IV HD. Complete remission (CR) was achieved in 29 of 30 patients with a stage I HD, 9 of 18 patients with stage II, 16 of 25 patients with stage III, and 9 of 23 patients with stage IV.

Conclusion: The most common subtype of HD was MC, followed, in order of frequency, by NS, LP and LD. Diagnosis of HD in more than 84 % of the cases was established late in its course (stages III and IV). CR was achieved in more than 64 % of the cases, including all stages and subtypes of HD.

**ANALYSIS OF MHC CLASS I EXPRESSION ON REED-STERNBERG CELLS IN RELATION TO THE CYTOTOXIC T-CELL RESPONSE IN EBSTEIN-BARR VIRUS POSITIVE AND NEGATIVE HODGKIN’S DISEASE**

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In order to get insight into the failure of the immune system to eradicate Epstein-Barr virus (EBV) harboring Hodgkin and Reed-Sternberg cells (H-RS cells), expressing the latent membrane protein 1 (LMP1), we analyzed MHC class I expression on H-RS cells in relation to the presence of activated cytotoxic cells, i.e. granzyne B expressing lymphocytes. H-RS cells in EBV positive cases of Hodgkin’s disease (HD) were found to express significantly higher levels of MHC class I heavy and light chain molecules as compared to EBV negative HD cases. When low levels of MHC class I expression were found (mainly in EBV negative cases), these were not associated with low levels of the transporter protein associated with antigen presentation 1 (TAP-1). The relatively high levels of MHC class I expression in H-RS cells in EBV positive HD cases were accompanied by significantly higher numbers of activated cytotoxic T-lymphocytes (CTLs) as shown by the presence of increased numbers of CD8 and granzyne B positive lymphocytes. However, these cells were only sporadically detected in the close vicinity of the H-RS cells.

These data suggest that other mechanisms than down-regulation of MHC class I or TAP-1 expression on H-RS cells are involved in the failure of the immune system to eradicate EBV harboring H-RS cells. Probably, the function of activated CTLs is locally inhibited by the H-RS cells or by reactive cells in the vicinity of the H-RS cells.

**EXPRESSION OF KI-A10 ANTIGEN IN HODGKIN’S DISEASE**

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Hodgkin’s disease (HD) is a malignant lymphoma of considerable heterogeneity. Even the REAL classification distinguishes four main subtypes: lymphocyte predominance (LP), nodular sclerosis (NS), mixed cellularity (MC) and lymphocyte depletion (LD). To analyze biological differences between these subtypes, we investigated 320 patients (pts) from three German pediatric treatment studies (HD-85, HD-90, HD-95). They included 183 boys and 137 girls with a median age of 12 years 9 months (range: 2 y 6 m to 21 y 2 m). In addition to CD30 and CD20, we applied the new antibody Ki-A10. This antibody detects a nuclear protein with a molecular weight of 24 and 28 kD in Hodgkin and Reed-Sternberg (HRS) cells. Its function is yet not known. In somatic tissues no Ki-A10 positive cells are found, in contrast to CD30.

As expected, most patients with LP expressed CD30 with occasional positive staining for CD20. In the remaining subtypes there was the opposite relation. Ki-A10 was positive in 133 of 230 pts (41.0 %) and occurred exclusively in neoplastic cells. There was a significant predominance of H-S (78 of 91, i.e. 85.7 %) compared to MC (27 of 35, i.e. 77.1 %) and LP (6 of 35, i.e. 17.1 %). Both pts with MLC were Ki-A10 positive. While there was no significant difference in Ki-A10 expression in stages II-IV, only a minority of stage I pts were positive. Comparing pts with A and B symptoms, there was no significant difference. However, Ki-A10 positivity was found more often in girls than in boys (70 of 137 vs. 62 of 183, p<0.000). The presence of Ki-A10 in pediatric HD had no adverse effect on the clinical course in this patient group.

5. Hodgkin’s Disease
Elevation of B-lymphocytes in Hodgkin's disease: a remission's phenomenon

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In a group of 68 patients with Hodgkin's disease (32 w., 36 m., station I to IV), the lymphocyte populations were tested. 58 (85%) patients have achieved a complete remission (CR). 85% of the patients with CR at least of one year duration showed an increased B-lymphocytecount (473 ± 237/μl). None of the 33 patients with a newly diagnosed Hodgkin's disease or in progressive disease showed any increase of the B-lymphocytes. The long observations of many patients could be helpful to determine the time of the B-lymphocytes' rising, at least 10 months after the end of the therapy. This increase is in 74% of the CR-patients a durable phenomenon (up to 16 years). This group is compared with a group of 112 patients with solid tumors. 41 (36%) patients had achieved a complete remission. 35% of these CR-patients showed an increased B-lymphocytecount (483 ± 161/μl). 10 of these 16 patients were treated with chemotherapy and radiotherapy, 4 with chemotherapy alone and 2 untreated patients.

A third group of 67 patients, as a control had an increase of the B-lymphocytecount (293 ± 114) in 20% of the cases only.

Conclusion: a durable increase of B-Lymphocytes in Hodgkin's disease after therapy seems to be a phenomenon of complete remission.

APOTOPSIS IN PERIPHERAL BLOOD T-LYMPHOCYTES OF PATIENTS WITH HODGKIN'S DISEASE

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The radiotherapy (subtotal body irradiation to the trunk of 7 patients with HD) was given at the 15 MeV linear accelerator, single dose 1-1.5 Gy to total dose 4-6 Gy as the first step of antitumor therapy. Apoptotic T-Lymphocytes (ATL) number was studied before and after radiotherapy. Furthermore, ATL in vitro before and after single irradiation of peripheral blood T-cells of 7 patients with HD and 10 healthy persons have been studied. The ATL number in patients with HD before therapy was 52.5±4.4%, in healthy persons - 17.2±1.9% (p<0.05). The ATL number in the patients with HD increased up to 98.0±5.8% (p<0.01) after radiation treatment. After in vitro irradiation of T-cells of HD patients the ATL number increased up to 90.0±9.0%, on the contrary the same irradiation increased the number of ATL only to 61.2±7.7% in healthy persons.

Conclusions:
1. The apoptotic peripheral blood T-lymphocytes number in patients with HD is higher in comparison with the data obtained for healthy persons.
2. Radiosensitivity of peripheral blood T-cells in pts with HD is higher than that in healthy persons.
RELATION BETWEEN EBV-SEROLOGY AND PRESENCE OF EBV IN THE HODGKIN AND REED-STERNBERG (HRS) CELLS OF PATIENTS WITH HODGKIN'S DISEASE (HD)

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BACKGROUND EBV is detectable in HRS cells in up to 50% of patients with HD. HD patients have also been reported to have higher serum levels against EBV antigens, also prior to the HD diagnosis and patients with high serum titers have a worse prognosis. The aim of the present study was to examine the relation between presence of EBV in the HRS cells and the antibody titers against several different EBV antigens.

RESULTS EBV was detected in 27/107 (25%) tumour specimens with a higher proportion among MC cases (61%) compared to negative. There were also no differences in the proportion of patients with detectable EBV in their HRS cells (EBV-positive) as compared to negative. There were also no differences in the proportion of patients with detectable or elevated VCA between the EBV-positive and negative patients. No expression of p80 was demonstrated in any case of HD.

DISCUSSION We were not able to demonstrate any relation between the presence of EBV in the HRS cells and the serum titers of various EBV antigens. The role of EBV in the development of HD and especially the relation to the immunologic response remains unclear.

EXPRESSION OF CD44 S AND VARIANT v6 ISOFORMS IN HODGKIN'S DISEASE; LACK OF PROGNOSTIC SIGNIFICANCE AND ASSOCIATION OF v6 POSITIVE LYMPHOCYTES WITH HRS CELLS. Jack FR, Taylor PRA, Cattan AR, Latham JA, McKenna D, Proctor SJ, Angus B, Dept Haematology, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK.

INTRODUCTION The transmembrane glycoprotein CD44 is a member of the hyaladherin family, widely expressed on hematolymphoid cells. It has important properties in lymphocyte differentiation, activation and homing, and has been implicated in metastasis and poor survival in several tumours including NHL. CD44v6, one of several alternatively spliced variants has a more restricted expression but has been shown to be an independent prognostic factor in lymphoma. We have identified 11 patients with poorly differentiated HD who have an univariate and multivariate analysis of clinicopathologic variables. The results of this analysis indicate that CD44v6 expression is not a significant predictor of survival in patients with HD.

RESULTS CD44v6 expression was assessed in 11/20 patients with HD. In 11/20 patients v6 was found in lymphocytes forming rosettes around HRS cells. Intense membrane expression of CD44v6 occurs in most HD cases. The role of CD44v6 in lymphocyte adhesion to HRS cells has not been studied in detail.

CONCLUSION CD44v6 is expressed in HD and may have a role in the pathogenesis of HD.
HODGKIN'S DISEASE, NODULAR SCLEROSIS: THE PROGNOSTIC SIGNIFICANCE OF MEDIASTINAL TUMOR SIZE

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1. Second Propedeutic Department of Internal Medicine, Athens University, Evangelismos General Hospital, Athens, Greece.
2. Larissa School of Medicine, Larissa, Greece.

Nodular sclerosis (NS) is the most commonly recognised histopathologic type of Hodgkin's disease (HD) with distinctive clinical and pathological features. Mediastinal involvement is common in NSHD while the tumor size of this presentation is considered of prognostic significance. To clarify the outcome of patients with NSHD according to the size of mediastinal involvement we reviewed our experience during the last 15 years. Between 1979-1994, 172 cases of HD were diagnosed and treated in our Unit; among them there were 104 cases (60.4%) of NS. The M/F ratio was 65/38 and the median age was 30 years (range 14-83).

For the purpose of this study patients were divided in 3 groups, according to the width of mediastinal mass (MM). Group A: patients with MM>1/3 the transthoracic diameter (24 cases -39%). Group B: MM<1/3 (40 cases - 38.5%). Group C: no mediastinal lymphadenopathy (40 cases - 38.5%). The stage distribution among the 3 groups was: Group A: stages I-II:12, Stages III-IV: 12, Group B: I-II: 21, III-IV: 19, Group C: I-II: 27, III-IV: 13 cases. The patients of the 3 groups were treated as follows: Group A: all cases received combination chemotherapy (CT) and radiation (RT), Group B: CT (31 cases), CT+RT (9 cases), Group C: CT (31 cases), CT+RT (8 cases), RT alone (3 cases). The complete remission rate among the 3 groups was: A: 95%, B: 92.5%, C: 90%. Analysis of survival curves showed that the survival at 6 years was 60% (A), 65% (B), 67% (C). These differences were not statistically significant.

In conclusion, the analysis of the cases with NSHD according to the width of the mediastinal mass indicates that the response rate to the initial treatment is high while the survival curves showed no significant differences between the 3 groups.

HODGKIN'S DISEASE IN NORTH INDIA: A SINGLE INSTITUTION EXPERIENCE

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In the last 15 years. Between 1979-1992, 262 cases of HD were diagnosed and treated in our Unit; among them there were 104 cases (60.4%) of NS. The M/F ratio was 65/38 and the median age was 30 years (range 14-83).

For the purpose of this study patients were divided in 3 groups, according to the width of mediastinal mass (MM). Group A: patients with MM>1/3 the transthoracic diameter (24 cases -29%), Group B: MM<1/3 (40 cases -38.5%). Group C: no mediastinal lymphadenopathy (40 cases -38.5%). The stage distribution among the 3 groups was: Group A: stages I-II:12, Stages III-IV: 12, Group B: I-II: 21, III-IV: 19, Group C: I-II: 27, III-IV: 13 cases. The patients of the 3 groups were treated as follows: Group A: all cases received combination chemotherapy (CT) and radiation (RT), Group B: CT (31 cases), CT+RT (9 cases), Group C: CT (31 cases), CT+RT (8 cases), RT alone (3 cases). The complete remission rate among the 3 groups was: A: 95%, B: 92.5%, C: 90%. Analysis of survival curves showed that the survival at 6 years was 60% (A), 65% (B), 67% (C). These differences were not statistically significant.

In conclusion, the analysis of the cases with NSHD according to the width of the mediastinal mass indicates that the response rate to the initial treatment is high while the survival curves showed no significant differences between the 3 groups.
Hodgkin's Disease in the Elderly: Clinical and Therapeutic Evaluation in a Cohort of 54 Patients.


Fifty-four patients over seventy years were treated for HD during 25 years. This population represents 7.2% of the whole Hodgkin's population and 45.7% of 118 pts over 60 years seen during this time with different approaches in the management and treatment according to different periods. Roughly before 1980 the treatment was conservative and thereafter curative when chemotherapy was more routinely used. The initial view of such patients has already been published (Cancer 1984; 53: 219: 2193). Since then we have managed 24 other patients with combined modality treatment using polychemotherapy and involved-field radiotherapy in early stages and poly- or monochemotherapy in advanced ones. This cohort includes 35 males (55.6%) and 9 females (33.4%) of 70 to 90 years; 35 stage IA (42.8%) and 19 (32.7%) stage IB/IIa; histologic type was mainly mixed cellularity (50%) then nodular sclerosis (27.8%). All but two had a lymphangiogram with no adverse effect, and the other staging tests were similar to those of younger people. The following table summarizes the main pretherapy characteristics of all patients according to the 2 periods:

<table>
<thead>
<tr>
<th>Period</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>50-69</td>
<td>28</td>
<td>7</td>
</tr>
<tr>
<td>70-84</td>
<td>15</td>
<td>4</td>
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<td>85-90</td>
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</table>

The Radiotherapy (RT) and Hematology (HE) Departments of the University of Florence (U) worked together in the management of HD during the last 20 years and decided to pool together their clinical material for analysis.

Results:

- The prognostic relevance of the substages of pathological stage III Hodgkin's disease (HD) and its clinico-therapeutic implications.


Owing to the good results obtained nowadays with the treatment of HD, a large number of long term survivors may be studied to better define "high risk" and "low risk" cases, to tailor treatment at presentation according to the available prognostic factors. Large series coming from single institutions include patients (pts) treated according to a more homogeneous clinical behaviour, and the resulting data analysis is therefore more accurate.

The Radiotherapy (RT) and Hematology (HE) Departments of the University of Florence (U) worked together in the management of HD during the last 20 years and decided to pool together their clinical material for analysis.

This report analyzes the effect of the different prognostic factors and of the therapeutic options adopted as presentations on survival (actuarial uncorrected, corrected and relapse free) and on the incidence of cardiac damage, for the stage III cases staged with laparotomy and splenectomy (pathologic stage, PS). In particular, the prognostic impact of the anatomic substaging (III I and II substages) of these patients will be analyzed.

Between 1970 and 1991, 261 pts have been treated at the U. Of them, 219 have been staged as PS III cases. The main clinico-therapeutic features of this subgroup are as follows:

- Gender: M 138, F 81; Age: <50 yrs = 184; >50 yrs = 33; Clin Stage: I = 10; II = 97; III = 122; Path. Stage (III I = 126, III II = 93.

Systemic symptoms: A = 154; B = 26; Histology: LP = 22; NS = 33; MC = 101; DL = 8; No subtype = 5; Treatment at presentation: III I pts: RT/CHT = 26; III II pts: RT; 24; RT+CT-T = 6; CHT = 31.

Among the 219 cases treated we observed 100 relapses; 49 patients deceased because of Hodgkin's disease, 51 have been salvaged with second line treatment.

- Complete remission (CR) was defined as the achievement of complete remission (CR) without the need for further treatment. However, the overall survival seems improved after 1980, perhaps due to a better management of pretherapeutic tests (diagnosis) and treatment. The usual exclusion criteria for elderly patients from trials provides no useful information about this kind of patient. The growing number of elderly in the general population justifies having more information about the management and treatment results of Hodgkin's disease and other malignancies in general.

IS IT COST EFFECTIVE TO TREAT HODGKIN'S DISEASE?

J. Novais, E. Watl, V. Angielii and J.A. C. Hoen.

Hodgkin's disease (HD) is today a highly curable disease. Several treatment modalities (RT, CHT, RT+CHT) with almost equal cure rates are available at different costs in the same population. We defined three periods: Before 1980, 1980-1990 and Since 1990, and calculated the loss in production, was given by the National insurance Association (NIA) and the hospital hotel stay 5%.

The Radiotherapy (RT) and Hematology (HE) Departments of the University of Tromso, the Radiotherapy (RT) and Hematology (HE) Departments of the University of Tromso, Norway.

Hodgkin's disease (HD) is today a highly curable disease. Several treatment modalities (RT, CHT, RT+CHT) with almost equal cure rates are available at different costs in the same population.


Department of Medical Oncology. Clinica Puerta de Hierro, Madrid, Spain.

In Hodgkin's disease (HD) today is possible to accomplish high rates of cure after treatment, even in advanced stages. We undertake the present study to determine the bad prognostic factors in our patients (pts).

- Patients and Methods: We reviewed retrospectively 367 pts with HD, diagnosed and treated in our hospital between January-1969 and December-1995. 137 pts were females (37.3%) and 230 pts (62.7%) were males. Median age was 31 years (SD: 14). By stages, 19.3% were IA, 2.2% IB, 22.7% II A, 13.1% II B, 10.9% III A, 10.1% III B, 3% IV A and 7.5% IV B.

Histologic studies showed nodular sclerosis (NS) 150 pts (40,9%), mixed cellularity (MC) in 126 pts (34%), lymphocytic predominant (LP) in 34 pts (9,3%), lymphocytic depletion (LD) in 41 pts (11,2%), and unclassified in 16 pts (4,4%). After the first line of treatment 343 pts (93,5%) achieved complete remission (CR).

Conclusions:

- The Cox proportional-hazards model was used for multivariate analysis and revealed the following values of relative risk (RR): no CR, RR 11 [confidence interval (CI) 95%, 6.3-20.9], age > 50 years, RR 4 (CI 95%, 2.5-6.8), LD, RR 2 (CI 95%, 1.3-3.6), B stages, RR 1.6 (CI 95%, 1.2-2.6). With a median of follow-up of 290 months the overall survival was 85% (0.2% relative error, RE) at 10 years, 76% (1.2% RE) at 15 years, and 70% (1.4% RE) at 15 years.

We conclude that to characterize bad prognostic factors can help to design special treatment strategies for these patients.
TREATMENT OF HODGKIN'S DISEASE IN ELDERLY PATIENTS

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The objective of the study was to explore the impact of age on responsiveness and tolerance to therapy and in the long run on survival. A retrospective analysis of the management of 45 patients older than 60 years was made. 26 patients were in stage I-II and 19 patients were in stage III-IV. 32 of 45 (71%) received treatment according to current protocols. Of 28 patients in early stage 19 received radical radiation therapy (RT), mantle or inverted Y, with a CR rate of 95% and 5-yr survival of 74%. The results were comparable with those below the age of 60, 88% and 82% respectively. 10 patients in stage III-IV and 3 patients in stage II received fulldoses of chemotherapy (CT), MOPPB/ABVD, with a CR rate of 70% and 5-yr relative survival of 31%. In the younger age group CR rate was 72% (20 of 28) and 5-yr relative survival 64% (18 of 28). 13 patients managed suboptimally only two (15%) are alive at 5 years. 5-yr relative survival for all patients treated with curative intent was 55% (16 of 32). A half of the patients showed poor tolerance to CT which required reduction of the dose or prolonging the interval of administration of the drugs. Our results suggest that: 1) Patients with adequate medical condition could be planned for standard therapy with curative intent, 2) Responsiveness and tolerance to RT is better than to CT, thus an age-adjusted CT schedule with additional local RT could be considered for those in advanced stage who do not fit for optimal treatment.

HODGKIN'S DISEASE IN PATIENTS AGED 70 YEARS AND OVER: A REGISTRY BASED ANALYSIS

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Between 1973 and 1993, 529 patients with Hodgkin's disease were entered into the Nottinghamshire lymphoma registry covering a population of 1.1 million. Twenty eight cases of immunohistochemically confirmed cases of Hodgkin's disease in patients aged 70 years or older were identified (3.5% of total). The male to female ratio was 1:1.5:1, but in the general population aged 70 years or over the ratio is 1:2:1 giving a corrected ratio of 1:2.1 (similar to patients aged less than 70 years). Of 14 patients in group 3 who, on account of their general condition, could be treated without dose reduction and achieved remission, show no difference with respect to duration of remission in comparison to the lower age groups. Therefore, in our opinion, a risk profile should also be drawn up for older patients, as they also, with appropriate therapy, can achieve long-term remissions.
RESULTS AND OWN EXPERIENCE WITH COMBINED MODALITY TREATMENT IN EARLY STAGES OF HODGKIN DISEASE WITH UNFAVOURABLE PROGNOSIS.

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It seems that combined modality treatment (CMT) is a method of choice in the management of early stages of Hodgkin disease (HD) especially for patients (pts) with bad prognostic factors (BPF) i.e. systemic symptoms (S), bulky peripheral tumor, mixed and depleted histology and ESR >60/0 ml. Reduction of irradiated volume and/or dose, or less number of chemotherapy (CT) cycles is a reasonable way to minimize acute and late side effects. In the period of 1986-1994 we have undertaken a prospective study on efficacy of "involved field" irradiation and MOPP CT. We enrolled to the study 49 pts in clinical stage I (S), II (S) and III (S). Tumor dose was 40 Gy followed by 5-10 Gy boost to bulky sites: cervical-supracavitary areas (75%), mediastinum (8%), inginal region (8%), axillary fossa (8%) and others (6%). Simultaneously 6-8 cycles MOPP CT were given. Median follow-up was 45.5 months (mte), SD±20, with range 4-144 months. DSS (Disease Specific Survival) mte was 91%, 77% and 66% mte for DFS (Disease Free Survival). The median survival time was 6.2 mte, and the range for DFS 1-9 years. The majority of pts (98.4%) achieved complete remission (CR) and had no relapse. Only 2% of pts relapsed. The majority of pts area was 12%.

Conclusions: the involved field irradiation and MOPP CT seems to be highly effective and safe method in the management of early stages of HD with BPF but larger material and longer follow-up is needed.

PROGNOSTIC FACTORS FOR EARLY STAGE HODGKIN'S DISEASE (HD).

MK Angelopoulou, TNP Vasikiskopoulou, F Kontopoulou, VA Boussiotis, A Paegalis. First Department of Internal Medicine, National and Kapodistrian University of Athens, Lalkon General Hospital, Athens, Greece.

Although, stage I and II HD is curable in the vast majority of the patients (pts), 20% of the pts relapse and a proportion of them actually die due to the disease or its complications especially secondary malignancies. The aim of the present study the determination of prognostic factors (PF) for complete remission (CR), disease-free survival (DFS) and overall survival (OS) for pts with clinical stage (CS) I and II HD. We analyzed 256 pts, who received their initial treatment in our Unit. The following parameters were investigated for their prognostic significance: Age, gender, CS, B-symptoms, histologic subtype, number of involved nodal sites (< vs ≥ 3), extranodal disease (E-disease), bulky disease (> 3 cm), pure lymphangitic disease, haemoglobin levels (< vs ≥ 11.0 g/dl), white blood cell count (< vs ≥ 10x10⁹/l), absolute lymphocyte count (< vs ≥ 2.1x10⁹/l), absolute eosinophil count (< vs ≥ 0.7x10⁹/l), ESR (< vs ≥ 20 mm/h) and serum albumin levels (< vs ≥ 3.0 g/dl). The endpoints of our analysis were CR, DFS and OS. The identification of PF for CR was performed by the x² test. Univariate analysis of PF for DFS and OS was performed by the log-rank test and multivariate analysis by Cox's regression analysis. The median age of our pts was 32 years (15-76) and 142/256 pts (56.3%) were males. 73 pts (29%) had CS I A (29%), 4 pts (2%) I B, 113 pts (44%) IIA and 66 pts (26%) IIB. Initial treatment Included only radiotherapy (RT) in 30 pts (12%). Most of CS IVA pts received chemotherapy (CT) predominantly MOPP, ABVD or EMB in combination with involved field RT of reduced dose (<3000 cGy). The vast majority of CS IIB pts received only CT (MOPP or MOPP/EVB or MOPP/EVIB) and CR was achieved in 5/6-2256 pts (98.4%). Five and 10 year survival rates were 84% and 80% for DFS and 92% and 80% for OS. No PF for CR were identified. E-disease adversely affected DFS (p=0.008). Univariate analysis of PF for OS demonstrated that age (> 60 or 41-60 vs 40 years p=0.00), pure Inflammatory disease (p=0.02) and ESR >20 (p=0.005) had adverse prognostic significance, but in multivariate analysis age proved to be the only PF for OS. Our data suggest that the already well established PF in early stage HD are not sufficient to distinguish pts with poor prognosis, who may have a major benefit from aggressive treatment.

RESULTS OF 3 ABVD AND SUBTOTAL NODAL IRRADIATION IN UNFAVOURABLE IA AND IIA HODGKIN'S DISEASE.


PURPOSE: To evaluate, in unfavourable IA and IIA Hodgkin's disease (HD), the results of 3 ABVD followed by subtotal nodal irradiation.

PATIENTS AND METHODS: From 1986-1991, 98 HD patients (pts) in stage IA and IIA were treated at diagnosis with 3 ABVD and subtotal nodal irradiation. All patients were clinically staged, and presented at least one of the following unfavourable prognostic factors: bulky mediastinal involvement, more than 3 involved nodal areas, ESR >40, extranodal "E" lesion. After 3 ABVD, a 36 Gy irradiation was planned (mantle field plus irradiation of spleen and upper paraortic nodes). A 6 Gy boost dosing (44 Gy in total) was added to the nodal area in which a residual disease was evident at the end of the 3 first ABVD.

RESULTS: 46 pts were male and 52 female. Mean age was 32 (range 14-65) with 17 pts older than 45 years. Histology was as follows: NS 80 and MC 18. Bulky mediastinum was present in 48 pts. The final complete remission rate (CR) was 94% in 83% the CR was already obtained after the first 3 courses of ABVD. The 5 year actuarial relapse free survival (RFS) was 90%. The most common side effect was leukopenia, hence we had to reduce dose of alkylating agents in 11% of cycles. There was no lethal complication.

Conclusion: the involved field irradiation and MOPP CT seems to be highly effective and safe method in the management of early stages of HD with BPF but larger material and longer follow-up is needed.

REDUCED COMBINED MODALITY TREATMENT FOR HODGKIN'S DISEASE: RESULTS OF A RANDOMIZED MULTICENTER TRIAL.

M. Herold, S. Siebert, K. Keilter and G. Anger for the EAST (HD).

Department of Internal Medicine, Klinikum Erfurt, D-99089 Erfurt, Germany.

In conclusion of a pilot-study presented previously we initiated a prospective randomised multicenter trial of a reduced combined radio-chemotherapy in Hodgkin's disease in limited stages with risk factors and in advanced stages.

Material and Methods: From 1/90 to 12/91 91 previously untreated patients entered the study. Treatment consisted of a hybrid-chemotherapy program utilizing cyclophosphamide/deversamustine in combination with vinblastin, procarbazine, prednisolone, doxorubicin, vincristin and bleomycin (6 cycles). Radiotherapy was sandwiched in between the chemotherapy courses and was given as an extended field radiation of 25 Gy.

Results: All patients are evaluable for the response to treatment; CR rate was 86%, 86% in the Ctx-group and 92% in the bendamustine-group respectively. The survival data at 5 years was 83% (CTX 80% vs. bendamustine 88%) and 87% (CTX 83% vs. bendamustine 91%). The advantages of the bendamustine-group are not statistically significant. The acute toxicity in both treatment arms is comparable and acceptable; concerning late toxicity up to now we did not observe any secondary leukemia or MDS.

Conclusion: We regard our treatment approach as useful, the results of the multicenter trial published by M. Herold et al. of our pilot study and it matches the reports of other groups using similar treatment policies.
COMPARISON OF MOPP AND A(E)BVD REGIMENS IN STAGE IIA AND IIA HODGKIN'S DISEASE.

MK Angelopoulou, ThF Vassalidakopoulos, F Kasotoglou, VA Boussiotis, GA Pangalia, First Department of Internal Medicine, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece.

The use of chemotherapy (CT) in combination with involved field radiotherapy (RT) for the treatment of early stage Hodgkin's disease (HD) has been investigated with concern in the present study. We analyzed 149 patients with classical stage (CS) IA and IIA HD. All patients had received CT (65 pts MOPP and 84 pts EBVD or ABVD with 400 mg of dacarbazine in combination with reduced dose (~3000 cGy) involved field RT. We aimed to compare the complete remission rate (CR), disease free survival (DFS), overall survival (OS) and incidence of myelodysplastic syndrome (MDS) between two groups of patients: the first group received MOPP and the second A(E)BVD. The two of the treatment arms did not differ significantly concerning their baseline characteristics, as indicated below.

<table>
<thead>
<tr>
<th>Patient's characteristics</th>
<th>MOPP (n=65)</th>
<th>A(E)BVD (n=84)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age (%&gt;60 years)</td>
<td>13.8</td>
<td>6.0</td>
<td>0.24</td>
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<td>Gender (males %)</td>
<td>66.2</td>
<td>54.8</td>
<td>0.16</td>
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<tr>
<td>Stage (% I, IA)</td>
<td>36.9/23.1</td>
<td>38/61.9</td>
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<tr>
<td>Histology (% LP, NS, MC, LD)</td>
<td>14.5/0.0/3.2/3.1, 16.7/51.2/3.2/1.0</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Pure lymphohistiocytic disease (%)</td>
<td>6.3</td>
<td>6.0</td>
<td>0.95</td>
</tr>
<tr>
<td>Extranodal disease (%)</td>
<td>6.3</td>
<td>6.0</td>
<td>0.92</td>
</tr>
<tr>
<td>RT (%)</td>
<td>87.7</td>
<td>92.9</td>
<td>0.30</td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CR (%)</td>
<td>98.5</td>
<td>100.0</td>
<td>0.25</td>
</tr>
<tr>
<td>DFS (5 and 10 yr, %)</td>
<td>79.2/77.7</td>
<td>92.3/94.0</td>
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</tr>
<tr>
<td>OS (5 and 10 yr, %)</td>
<td>85.7/71.2</td>
<td>92.3/94.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Secondary MOPP/ANLL (%)</td>
<td>3</td>
<td>0</td>
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</table>

CR rates and OS did not differ significantly between the two treatment groups, although there was a trend towards better OS for EBVD or ABVD treated pts. Furthermore DFS of EBVD or ABVD treated pts was significantly longer. A(E)BVD proved to be no less oncogenic in our study with a median follow-up of 7.5 years. Patients with CS I/A II HD are successfully treated with the A(E)BVD regimen with a reduced dose of Dacarbazine combined field RT of limited dose. The results appear to be superior to dose with MOPP, which in addition is more toxic.

B.N.L. PILOT STUDIES OF NEO-ADJUVANT CHEMOTHERAPY IN CLINICAL STAGE IIA AND IIA HODGKIN'S DISEASE.

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Hodgkin's disease CSIA and IIA can be managed with mantle radiotherapy. However, the relapse rate at 5 years is approximately 40%, this can be reduced either by extended-field radiotherapy or chemotherapy. We now report a pilot study of MVP (Metothrexate, Vinblasine and Prednisolone).

Patients received 2 cycles of chemotherapy and then were assessed for response by WHO criteria prior to involved field radiotherapy followed by 4 further cycles of chemotherapy. The table below shows that response was seen in 92% of patients. There were 4 cases of pneumonia (10%) and 3 of sepsis.

MVP is less toxic than VBM but still represents a considerable burden of treatment for the patient as an adjuvant to radiotherapy because treatment lasts for 9 months. We are therefore now exploring shorter treatment protocols.

<table>
<thead>
<tr>
<th>RESPONSE RATES</th>
<th>VBM</th>
<th>MVP</th>
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<tbody>
<tr>
<td>Eligible</td>
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<tr>
<td>CR</td>
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<td>NC</td>
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<td>2</td>
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<tr>
<td>Progression</td>
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</table>

Between 1979 and 1995 125 previously untreated patients with advanced Hodgkin's disease were treated with anthracycline containing combination chemotherapy (66 ABVD, 47 COPP/ABV hybrid, 12 alternating COPP/ABVD). The median age was 34 years. The male to female ratio was 84:1. 41 patients were in clinical stage III and 84 in stage IV. More than half of the patients (76%) had systemic symptoms. In 72 (57.8%) cases complete remission, in 16 (12.7%) partial remission was achieved. 35 (29.5%) patients did not respond to treatment. Mean time of remission was 59.6 months in CR, 12.1 in PR group. The mean overall survival was 69.4 months in CR and 28.5 in PR. The mean overall survival of non responding patients was 19.4 months. Life threatening complications or severe side effects were not observed. Effectivity and characteristics of different anthracycline containing regimens will be presented in details.
THE EFFECT OF COMBINED TREATMENT OF ABVD+ IRRADIATION VERSUS COPP (MOPP, LOPP) WITH PATIENTS IN II CLINICAL STAGE OF HODGKIN'S DISEASE

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During the period from 1985 to 1995 a group of 70 patients (pts) in II clinical stage (CS) of Hodgkin's disease (HD) were treated. The average age of patients was 37 years (15-65), 28 female and 42 male patients. They were treated according to two basic protocols - ABVD+ irradiation (ADY 25 mg/m² d1,15 day, Bleomycin 10 u/m²,1,15, Vinblastin 6 mg/m²,1,15, DTIC 75 mg/m² d1,14) at 28th day in three cycles, irradiation according to Kaplan (40-44 Gy), or COPP (LOPP/MOPP), (Endoxan 600 mg/m² 1-14 days, Vincristine 1 mg/m² 1,14, Procarbazine 100-150 mg 1-14 days, Prednisolone 40 mg d1-14 day, versus Chlorambucil 6 mg/m² p.o. 1-14, or Mustine 6 mg/m² 1,14). Twenty-eight patients (40%) were treated with ABVD+ irradiation, while the rest of 42 patients (60%) were given COPP (LOPP or MOPP). Among the patients treated with ABVD-irradiation 8 patients (11%) manifested a bulky tumor mass in mediastinum and were managed separately. Out of 20 (71%) patients in CS II of HD who were treated with 3 series of ABVD+irradiation a complete remission (CR) had been achieved in case of 17 (85%) patients while partial remission (PR) was accomplished in case of 3 (15%) patients. In case of 8 (33%) pts. manifesting bulky tumor mass in mediastinum complete remission with 3 cycles administration was realized with 5 patients and PR with 3 patients. In the group of 42 (60%) II CS patients treated with COPP, the remission was achieved after 6 cycles in case of 25 (60%) patients and PR in case of 17 (40%) patients. Correlation of CS patients treated with COPP, the remission was achieved after 6 cycles in case of 3 (15%) patients. In case of 8 (15%) pts. manifesting bulky tumor mass in mediastinum complete remission with 3 cycles administration was realized with 3 patients and PR with 2 patients. Out of 28 ABVD+irradiated patients 17 (60%) pts. were treated with radiation alone, 5 with combined modality and 22 with chemotherapy alone. Complete remission rate was 84%, identical, in both groups. But relapse occurred in 14/57 pts of ID group, significantly higher than in pts of SD group (38% vs 25%) and the time to failure was shorter (mean 13.5m vs 29.7m). In pts with stages I-II, radiotherapy alone failed in 4/13 pts, compared to 11/20 pts treated with combined modality. Six of 14 pts were salvaged by 2nd-line therapy and remained free of disease. Thus, 10 years survival of ID group was 96%, comparable to that of SD group (75%). In conclusion, ID presentation of HD has poorer prognostic features (age and systemic symptoms) compared to SD presentation. Nevertheless, the outcome of patients with ID disease who are properly treated is not different than those with SD disease.

IMRADIAPIHRAGMATIC (ID) HODGKIN'S DISEASE (HD): CLINICAL FEATURES, TREATMENT AND OUTCOME

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Forty four patients (pts) with ID presentation of HD were treated at NIOC during the years 1978-1992. We compared them to 280 pts with originally supradiaphragmatic (SD) disease who were treated over the same period. The ID group was older (mean age 42 y vs 32 y), its M:F ratio was higher (0.68 vs 0.37) and B symptoms were more common (66% vs 41%). Mixed cellularity and lymphocytic depletion were the predominant histological types and were associated with advanced age, B symptoms and retroperitoneal disease. Stage distribution was similar in both groups. Thirty three (75%) of 44 pts with ID disease were at stages I-II, 4 - stage III and 7 - stage IV. Seven pts were treated with radiotherapy alone, 14 with combined modality and 22 with chemotherapy alone. Complete remission rate was 84%, identical, in both groups. But relapse occurred in 14/57 pts of ID group, significantly higher than in pts of SD group (38% vs 25%) and the time to failure was shorter (mean 13.5m vs 29.7m). In pts with stages I-II, radiotherapy alone failed in 4/13 pts, compared to 11/20 pts treated with combined modality. Six of 14 pts were salvaged by 2nd-line therapy and remained free of disease. Thus, 10 years survival of ID group was 96%, comparable to that of SD group (75%). In conclusion, ID presentation of HD has poorer prognostic features (age and systemic symptoms) compared to SD presentation. Nevertheless, the outcome of patients with ID disease who are properly treated is not different than those with SD disease.

HODGKIN'S DISEASE CLINICAL STAGES III with BULKY TUMOR AND IV: 3-YEAR RESULTS OF HD-MA COMPARED WITH POFI-PROTOCOL


10-year results of the POF1 protocol (1981-1988) showed that survival (Sv) and freedom from progression (FFP) of patients (pts) with Hodgkin's disease treated by 3 ABVD (cumulated doses, mg/m²: Adriamycin 150, bleomycin [BLM] 60, vinblastin [VLB] 34, dacarbazine 2250, plus methylprednisolone [MP] 1200) cycles followed by (subtotal) lymphoid irradiation (TLI) was lower is pts with a bulky tumor mass (mediastinal mass > 45 and/or humbo-soriclt-pelvic involvement [B-s] pts), compared with B-s pts [ICO, 1996, in press]. Therefore B-s and clinical stage (CS) IV pts were treated by a 6-drug combination (randomization in 3 or 4 cycles over 3 months with similar cumulated doses, mg/m²: cyclophosphamide 4000, etoposide 2400, vincristine 4, VLB 18, etoposide 900, methotrexate 180, plus MP 1500) followed by the same TLI (protocol HD-MA [1990-1995]; evaluation for pts included as of 31/12/94).

Initial characteristics of pts were the following ones: POF1 (141 pts) sex M 59, P. 41; age <40 y 65, >40 y 35; B symptoms 67; CS I-III .61, IV .49; histology nodular sclerosis (NS) 60, mixed cellularity (MC) .23, others 15; HD-MA (109 pts) sex M 67, P. 33; age <40 y 55, >40 y 54; B symptoms 49; CS I-III .51, IV .49; histology NS-55, MC-38, others .17. Results as follows (N): POF1: complete remissions (CR) post-CT/post-RT 55/86, for CS III .66/85, for CS IV .53/87; 3-y Sv/FFP 63/70, for CS III .85/80, for CS IV .78/73; HD-MA: CR post-CT/post-RT .53/83, for CS III .57/95, for CS IV .59/76; 3-y Sv/FFP 62/72, for CS III .86/81, for CS IV .75/62. No significant differences between these two protocols. A more intensive chemotherapy should be tested to improve Sv and FFP in these high-risk pts.

Objective: To determine the appropriate irradiation dose after modern polychemotherapy in patients with intermediate stage Hodgkin’s disease (HD) Methods: HD patients in stage I to IIIA with large mediastinal mass, extranodal disease or massive extension involvement were treated with two double cycles of alternating COPP/ABVD followed by EF irradiation in two successive trials of the GHSG. In the first trial (HD93-RR) 146 patients responding to 2x COPP/ABVD were randomized to receive either 20 GY (70 patients) or 40 GY (76 patients) EF irradiation in non-bulky areas; a cohort of 111 patients fulfilling the same inclusion criteria in the subsequent trial (HD98-03) were treated with 30 GY EF irradiation in non-bulky areas. Initial bulk only always received 40 GY. Results: Freedom from treatment failure (FFTF) and survival (SV) curves are superimposable in the randomized as well as historical comparison. 40 GY

A randomized Phase II study (HD94) compared low-risk HD patients (age < 45 yrs) with 37 males and 2 females. Histological subtype according to the Rye classification was not available. Histological subtype was not available. Histological subtype was not available.

The treatment has been well tolerated. There is not at the moment any significant difference between the two types of treatment options, but the follow-up is insufficient to detect a possible difference between the two radiation options to evaluate the relapse risk and overall long-term toxicity.

Objective: Validate the prognostic model reported by the Memorial Sloan Kettering Cancer Center (Stress JCO: 1173-1186, 1990).

Patients and Methods: Eligible patients (pts) enrolled in the ongoing multicenter study (0895 protocol). Pts aged under 66, with clinical stage III/Ib-IV and randomized to detect 6 cycles of chemotherapy with 0CSF support. A detailed LDH, 

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival</th>
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<tr>
<td>I</td>
<td>83%</td>
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<tr>
<td>II</td>
<td>63%</td>
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<tr>
<td>III</td>
<td>45%</td>
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<tr>
<td>IV</td>
<td>20%</td>
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Results: 14 pts fulfilled the required criteria. The percentage of pts with unfavorable characteristics were: age > 45 yrs 20%, elevated LDH 44%, anemia 43%, inguinal involvement 15%, mediastinal mass > 45%.

Analysis of prognostic factors using the Cox model for overall survival showed the following relative risk (RR): age RR = 5.58 (p = 0.005), anemia RR = 2.70 (p = 0.0028), LDH RR = 2.51 (p = 0.0063). After a median follow-up of 36 months overall survival and event-free survival are estimated to be 80 ± 4% and 76 ± 5% respectively. Results according to the subgroups are as follows:

Factors | Points | 0 yrs | 3-yrs | 5-yrs | DFS
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<tr>
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<td>Age</td>
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<td>0</td>
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<td>73</td>
<td>72</td>
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</table>

The Cox model for overall survival showed the following relative risk (RR): age RR = 5.58 (p = 0.005), anemia RR = 2.70 (p = 0.0028), LDH RR = 2.51 (p = 0.0063). After a median follow-up of 36 months overall survival and event-free survival are estimated to be 80 ± 4% and 76 ± 5% respectively. Results according to the subgroups are as follows:

Factors | Points | 0 yrs | 3-yrs | 5-yrs | DFS
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</table>

CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) is a standard chemotherapy protocol for patients with advanced stage HD.

<table>
<thead>
<tr>
<th>EB</th>
<th>CR</th>
<th>PR</th>
<th>Failure-Free Survival Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>97</td>
<td>128</td>
<td>79% (at 2 yr) 68% (at 3 yr) 51% (at 3.5 yr)</td>
</tr>
<tr>
<td>1</td>
<td>76</td>
<td>59</td>
<td>96% (at 2 yr) 91% (at 3 yr) 81% (at 3.5 yr)</td>
</tr>
</tbody>
</table>

We conclude that CHOP shows sufficient promise to warrant additional investigation, particularly using higher doses of cyclophosphamide and etoposide with GCSF support.
ETOPOSIDE AND EBIRUBICIN CONTAINING CHEMOTHERAPY AND DOSE REDUCED RADIOTHERAPY IS A HIGHLY EFFECTIVE TREATMENT OF HODGKIN’S DISEASE WITH LOW TOXICITY.

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Due to advances in chemotherapy and radiation, Hodgkin’s disease is a model for a curable malignancy. Secondary tumors and long-term toxicity after the successful treatment are an important late event and still must be reduced. The question has to be raised how to accomplish reduction in toxicities without sacrificing the excellent responses that have been achieved. Patients and methods: A modified ABVD-scheme, the EBOEP-regimen, containing epirubicin (E), bleomycin (B), vincristine (O), etoposide (E) and prednisone (P) was used in the treatment of patients with Hodgkin’s disease in an attempt to reduce acute and long-term toxicity of a combined chemo- and radiotherapy. 56 previously untreated patients with stage I, II, and unfavourable prognostic factors (38 pts.) or with stage III (18 pts.) received EBOEP followed by radiotherapy. Results: Complete remission was achieved in all cases. The actuarial overall survival rate at 5 years was 94.1% (95% CI 85.1% to 95.9%), the relapse free survival rate was 88.5% (95% CI 77.9% to 95.2%) after a median observation period of 5.5 years. Acute toxicity was low. Only 7 patients developed WHO-grade 4 leukenopia and 2 patients developed grade 4 chemo toxicity. Due to potentially reversible myelosuppression in every case the first 3 cycles could be delivered in a median time of 56 days. Epirubicin, bleomycin and etoposide were administered in full doses in at least 94% of all chemotherapy-cycles. The most frequent non-hematologic side effect was peripheral neuropathy, which was the reason for vincristine attenuation in 11 1% of all cycles. Echocardiography, lung function testing and semen analyses demonstrated that EBOEP plus radiotherapy implies a minimal risk for long-term complications regarding organ functions. Myelodysplastic syndromes or acute leukemias did not occur so far after a median observation period of 5.5 years (minimum 2.4 years). Two solid tumours (parotid gland, colon) were observed. Conclusion: The study demonstrates that EBOEP is a well-tolerated regimen with a high rate of drug delivery. EBOEP has the potential to offer equal antitumour activity to other regimens in terms of remission induction and overall survival with a low risk of long-term toxicity.

MOPP/ABV HYBRID: TREATMENT OF HIGH RISK Hodgkin’s DISEASE (HD).

EXPERIENCE OF A SINGLE CENTER OVER A SIX - YEAR PERIOD.

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There is theoretical and empirical evidence for the superiority of alternating and hybrid MOPP/ABV (=D) combinations to standard four drug chemotherapy for HD. From July 1990 to January 1995, 42 patients (pts) with newly diagnosed high risk HD (advanced stage, bulky disease, B symptoms) were treated with MOPP/ABV hybrid combination chemotherapy.

Median age at presentation was 31 yrs (range 15 - 72). Nodular sclerosis was the predominant histologic type (71%). Eighteen pts (43%) had advanced stage disease (III, IV). 18 (43) had B symptoms and 14 (33%) had bulky disease (nodal mass >10cm or M/T ratio >3/3). However, eight pts with stage IIa have also been included in the study. Pts in CR after six cycles received two more cycles of hybrid combination while those with previous bulky disease received RT. The median number of MOPP/ABV cycles administered was 7 (range 3 - 8). Sixteen pts (38%) received complementary RT to sites of previous bulky disease or to an osseous involvement (two pts).

At the completion of chemotherapy, thirty eight pts (90%) achieved CR (Gallium scan negative in pts with large mediastinum) and four pts failed to respond (PR: 1, NR: 3). Four pts had recurrent disease (2/8 with large mediastinum). Four pts have died with active HD. With a median follow-up of 25 months, actuarial overall and progression-free survival (PFSS) at 5 years was 65% and 74% respectively. Disease free survival (DFS) for 38 complete remitters was 82% at 4 yrs. Age, histology, stage, bulky disease, bulky mediastinum and ESR were of no prognostic significance for PFSS. Bulky mediastinum was a negative prognostic factor for DFS (P<0.007). Hodgkin’s toxicity and infections (grade 3, 4) occurred in 60% and 50% of pts respectively. From 19 pts <50 yrs old experienced severe (grade 4) infections compared to 0/2 pts >40 yrs old (P<0.05).

Hybrid MOPP/ABV is effective chemotherapy for high risk HD, however with considerable toxicity (hematologic - infections), especially in older patients. Growth factors may therefore prove useful. Bulky mediastinal disease remains a therapeutic challenge.
STAGE IV HODGKIN'S DISEASE: RESULTS OF ALTERNATED (MMMA) AND HYBRID (MAMA) MOPP-ABVD REGIMENS.


The Italian Hodgkin's Disease Registry (PIHDR) + U.O. of Hematology - Ospedale Civile - Arezzo - Italy.

PURPOSE: To study the outcome and the prognostic factors of stage IV Hodgkin's disease (HD) patients (pts) treated with alternated chemotherapy regimens.

PATIENTS AND METHODS: From 1982 to 1993, 116 stage IV untreated HD pts were treated at diagnosis with an alternated chemotherapy regimen. 42 pts were treated with the alternated MOPP/ABVD (MMMAA), and 75 pts with the hybrid 1/3 MOPP - 2/3 ABVD (MAMA) regimen. Both chemotherapy regimens were scheduled as originally proposed by Bonadonna et al. The pts in complete remission (CR) after the first 3 courses of chemotherapy had only 6 courses, while late responders had 3 courses more for a total of 9 courses. Radiotherapy (36 Gy) was only planned on bulky areas. Pts were retrospectively stratified on the basis of the radiotherapy actually done in the pts treated according to the initial plan versus those treated with a more intensive radiotheraphy (mainly because a slow response to chemotherapy of some nodal areas).

RESULTS: Mean age was 41, with 43 pts (77%) older than 45 years. The clinical features at diagnosis were distributed as follows: Sex: NS 50%, MF 38%, LD 12%; B symptoms 60% - hepatic involvement 28% - lung involvement 21% - bone marrow involvement 15% - cervical lymph node involvement 16% - more than one extranodal involvement 22% (23 pts (43%)) underwent an extensive radiotherapy. CR was obtained in 88 pts (75%). The 10 year actuarial relapse free survival (RFS), overall survival (OS) and event free survival (EFS) rates were 64%, 55% and 45% respectively. No statistical differences were seen in CR, RFS, OS of EFS between MMMAA and MAMA pts.

The prognosis was not statistically influenced by any tested variables (sex, systemic symptoms, number of extranodal involved sites, histology, more extensive radiotherapy). The pts older than 45 years had a worse survival than younger ones (CR vs 60% vs. 75%, p<0.05), but this difference was at least in part HD unrelated, as demonstrated by the absence of differences in CR, RFS and freedom from progression rates between younger and older pts.

CONCLUSIONS: The overall cure rate of stage IV untreated HD pts treated with conventional alternated regimens is not more than 50%. No differences were seen between MMMAA and MAMA regimen so far we could not find any clinical variable that can predict the group of pts at higher risk of failure.


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Departments of Oncology, Hematology and Social Medicine, Hadassah University Hospital, Jerusalem, Israel.

Between 01/01/1990 and 31/12/1993, 60 patients with advanced Hodgkin's Disease (23 men and 37 women) received with MOPP-ABV in our institution. Follow up was 6-108 months (median 35 months). Ages ranged from 14 to 71 (median - 30). At diagnosis 45.8% of the patients presented in stages I (bulky) and II, 11.5% stage III, and 18.6% stage IV. 63.3% had B symptoms. Histology: 40 patients (66.6%)- nodular sclerosis, 9 - Mixed Cellularity, 3 - Lymphoepithelial Predominance, 4 syncytial variant and 4 unknown. Six patients underwent staging laparotomy. 69% received 6 courses (range 3-8). 37 patients (61.7%) received additional radiotherapy, including 36 in a mantle field (median dose 3040 cGy). Toxicity included at least one episode of febrile neutropenia in 30 patients (50%), and 1 death during treatment. No other Grade IV toxicity was noted.

Response: 43 patients (72.8%) achieved CR, 11 patients (19.6%) PR >50%, 1 patient died, and 1 was not evaluable. Atainment of CR was not associated with stage. Overall 5 year survival (5YS) was 73%; with 81% in the 14-29 age group, 75% in patients aged 30-44, and 53% in those aged 45 and more (P>0.05). Patients who received their treatment on schedule (39 patients) had significantly improved 5YS compared to those with treatment delays (p<0.05). 5 year failure-free survival (FFS) was 57%. Two patients, both of whom received combined modality therapy, died of secondary leukemia/MDS.

We conclude that MOPP-ABV is an effective regimen for advanced Hodgkin's Disease in our setting. However, because of reports of equivalent efficacy and decreased leukemogenesis associated with ABVD, we have returned to the latter regimen in our current cohort of patients.

HYBRID MOPP/ABVD VS HYBRID MOPP/ABVD PLUS G-CSF IN HODGKIN'S DISEASE (HD).


1. Dept of Medical Oncology, 2. Department of Pediatric Hematology, University of Padova, 3. Department of Medical Oncology, 4. Department of Pediatric Hematology, University of Bologna, 5. Department of Medical Oncology, 6. Department of Internal Medicine, University of Padua, 7. Department of Urology, 8. Department of Internal Medicine, University of Bologna, 9. Department of Pediatrics, 10. Department of Pediatrics, University of Padua, 11. Department of Internal Medicine, University of Bologna, 12. Department of Internal Medicine, University of Bologna, 13. Department of Medical Oncology, University of Padua.

From November 1992, 49 patients (pts) with advanced HD were enrolled in a multiinstitutional randomized trial, comparing hybrid MOPP (on days 1 to 7) / ABVD (on day 13) plus G-CSF (arm A) to hybrid MOPP / ABVD without G-CSF (arm B). G-CSF 300 μg/die s.c. was administered on days B-8 and ABVD on days 2-11 after MOPP and on days 2-12 after ABVD, if the absolute neutrophil counts (ANC) reached 10,000/μl. The pts were treated in 36 pts (75%) receiving 6 courses (range 3-8). 37 patients (61.7%) received additional radiotherapy, including 36 in a mantle field (median dose 3040 cGy). Toxicity included at least one episode of febrile neutropenia in 30 patients (50%), and 1 death during treatment. No other Grade IV toxicity was noted.

CONCLUSIONS: The overall cure rate of stage IV untreated HD pts treated with conventional alternated regimens is not more than 50%. No differences were seen between MMMAA and MAMA regimen so far we could not find any clinical variable that can predict the group of pts at higher risk of failure.

COMPARISON OF ALTERNATIVE MOPP/(E)BVD AND HYBRID MOPP/(E)BV IN THE TREATMENT OF ADVANCED HODGKIN'S DISEASE (HD). A. Barbuquelea, ThP Vassilakopoulou, MA Angelopoulou, F. Kostopoulou, M. Hatizoglou, VA Bouasanta, GA Pangella. First Department of Internal Medicine, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece.

The alternating administration of MOPP and (E)BVD (MOPP/(E)BVD) as well as the more intense hybrid MOPP/(E)BV regimens, have seen both standard options for the treatment of advanced HD stages. In the present study we analyzed 134 patients (pts) with HD, who received their initial treatment with MOPP/(E)BVD or MOPP/(E)BV in our Unit. 85 pts were treated with alternating MOPP/(E)BVD and 39 with the hybrid MOPP/(E)BV. Of the pts treated with MOPP/(E)BVD, 66 had been scheduled to receive 12 (6+6) cycles as opposed to 6 (3+3) cycles for the remaining 19 pts. The median age of our pts was 34 years (14-71) with 76/14 (61%) males and 12/70 (17%) females. They were of stage I (26%), II (32%) and IV (41%) disease. Patients treated with the alternating regimen did not differ from those treated with the hybrid one, with respect to age, gender, B-symptoms, histologic subtype, nodal and total number of disease sites.

The endpoints of our analysis were the achievement of complete remission (CR) and the duration of disease free survival (DFS). Comparisons between MOPP/(E)BVD and MOPP/(E)BV were based on x² and log-rank tests. The following table summarizes the efficacy of the two regimens which seems to be identical.

<table>
<thead>
<tr>
<th>CR (%)</th>
<th>MOPP/(E)BVD</th>
<th>MOPP/(E)BV</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>5 yr DFS</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>5 yr EFS</td>
<td>73</td>
<td>74</td>
</tr>
<tr>
<td>5 yr OS</td>
<td>72</td>
<td>72</td>
</tr>
</tbody>
</table>

The alternating MOPP/(E)BVD and hybrid MOPP/(E)BV regimens seem to be equally effective in the treatment of advanced HD disease stages.

5. Hodgkin's Disease
HYBRID MOPP/EBVD +/- MEDIATIONAL RADIOThERAPY FOR ADVANCED HDGKIN'S DISEASE.

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Aims. To test the activity and toxicity of hybrid MOPP/EBVD, a slight modification of Klimo's MOPP/ABV hybrid program, without DTC detection and with substitution of Etoposide (Eto) for Doxorubicin (Dox).

Methods. Sixty consecutive pts affected by advanced Hodgkin's disease (M/F=13/27; median age 30, range 16-70; Stage II B and/or bulky = 16; Stage III=12; Stage IV=12; L/P=14; NS=26; MC=20). Twenty-five (42%) of them presented with bulky mediastinal enlargement (median M/T=0.42, range 0.34 - 0.60) and 16/30 (52%) with B symptoms.

Results. The early remission rate was 90% for HN2-PCZ and 81% for HDV + CCNU in all cycles was 0.90 for HN2-PCZ and 0.87 for HDV + CCNU. After a 32 mo. median follow-up the 7-year dose density (ADD) actually delivered in all cycles was 0.90 for HN2-PCZ and 0.87 for HDV + CCNU. Sixty consecutive pts affected by advanced Hodgkin's disease (M/F=13/27; median age 30, range 16-70; Stage II B and/or bulky = 16; Stage III=12; Stage IV=12; L/P=14; NS=26; MC=20). Twenty-five (42%) of them presented with bulky mediastinal enlargement (median M/T=0.42, range 0.34 - 0.60) and 16/30 (52%) with B symptoms.

Conclusions. Hybrid MOPP/EBVD +/- mediastinal RT is effective with a moderate acute toxicity. It allows adequate doses of drugs to be delivered and enables to achieve high CR, OS, EFS and RFS rates. Our results are in keeping with those of other similar studies.
LONG-TERM RESULTS AND PROGNOSTIC FACTORS IN 106 PATIENTS WITH HODGKIN'S DISEASE IN FIRST RELAPSE

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From September 1971 until June 1994, 623 patients (pts) with newly diagnosed Hodgkin's disease (HD) were referred to our department. Initial treatment consisted of combination therapy (CT) alone for 20% of the pts, chemotherapy (CT) alone for 30%, and combined modality therapy (CMT) for 50%. Stage at diagnosis was stage IIA/B in 14% of pts, stage IIB in 10% of pts, stage III in 14% of pts, and stage IV in 53% of pts. Six hundred and ten pts (10.4%) experienced a secondary neoplasm (8 solid tumors, 3 hematological tumors) during a median follow-up of 9.3 yr, 5 and 10-yr overall survival (OS) were 45% and 33%. Median OS was 3.7 yr. Among the 70 pts in second CR, respective 5 and 10-yr disease-free survival (DFS) were 49% and 38%, respective 5 and 10-yr HD-free disease survival (HDFS) were 61% and 55%. Eleven out of the 106 pts (10.4%) experienced a secondary neoplasm (8 solid tumors, 3 hematological tumors). In a univariate analysis, a bad OS was associated with the following parameters at relapse: age < 40 (p < 0.001), favorable performance status (p < 0.001), early stage (p < 0.001), absence of bulky lymphadenopathy (p < 0.001), absence of B symptoms (p < 0.001), absence of stage (p < 0.001), and absence of treatment failure (p < 0.001). Using a multivariate analysis, the only independent favorable prognostic factors at relapse were first CR duration > 12 months (p = 0.03). Using a multivariate analysis, the only independent unfavorable prognostic factors at relapse were first CR duration < 12 months (p = 0.03), and absence of lymphadenopathy (p = 0.03). A retrospective study, with a long follow-up, confirms that one third of HD pts in first relapse can be cured with conventional salvage therapy.

INDEX OF PRE-TREATMENT INTENSITY PREDICTS THE OUTCOME AFTER HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS PROGENITOR CELL SUPPORT IN PATIENTS WITH RELAPSED HODGKIN'S DISEASE

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Patients (pts) with Hodgkin's disease (HD) relapsing after adequate systemic therapy have a poor prognosis with conventional salvage therapy. High-dose chemotherapy with autologous progenitor cell support (HDC) has gained wide acceptance because of superior results in a randomized study. However, subsequent relapses do occur. We analyzed our pts with relapsed but still chemosensitive HD in order to define factors associated with poor outcome after HDC. Between 1988 and 1995 40 pts received HDC according to the CBV regimen. With a median follow-up of over 3 years, the 3-year survival was 63%, the event-free survival (EFS) 45%. By log-rank analysis conventional parameters, including stage, extranodal disease, bone marrow infiltration, and B-symptoms did not influence EFS. The number of chemotheraphy regimens or the duration of the last remission prior to HDC did influence short-term EFS but not long-term EFS. To better define the treatment intensity that should reflect the aggressiveness of HD, we developed an index of pre-treatment intensity (IPI) defined as: IPI = 365 * (number of different chemo- and radiotherapies delivered per 1000 * number of different chemo- and radiotherapies delivered per 1000 * number of years from diagnosis to start of HDC). IPI thus gives an average number of therapies delivered per year during the time from diagnosis to start of HDC. Median IPI was 1.09 (range 0.24-6.73). Dividing pts into 3 groups of similar size according to their IPI (IPI < 0.9, N = 16; IPI = 0.9 - 1.5, N = 11; and IPI > 1.5, N = 13) lead to highly significant survival differences with an EFS of 16%, 45%, and 84% respectively (p < 0.001). Median EFS was 13 and 30 months for the poor and medium risk pts, while good risk pts showed a plateau at 84% even five years after HDC. Dividing patients into 2 groups (IPI > 1.2 versus IPI < 1.2) results in an EFS of 16% versus 68% with a median of 14 months for the high-risk group and a plateau at 68% for the low-risk group (p < 0.001). We propose the IPI as a valuable discriminator for the prognosis after HDC and recommend its validation in other series of pts with relapsed Hodgkin's disease treated with HDC.

RISK FACTORS FOR RELAPSE IN YOUNG PATIENTS WITH ADVANCED HODGKIN'S DISEASE


Objective: To study disease features at diagnosis in order to predict relapse once complete remission (CR) is achieved, and therefore setting up the basis for consolidation.

Background: Risk factors to predict for poor survival in Hodgkin's disease has been studied and found to coincide with those of induction failure. Thus, the latter would be a good selection criteria for high dose therapy with hematopoietic support.

The present study has been conducted to search for predictive factors for relapse in patients with advanced disease in CR after first line induction therapy, belonging to the first peak of the bi-modal age distribution.

Material and methods: Seventy-five patients from four hospitals in Catalonia have been gathered since 1976 till 1999, providing a minimal follow up of 1 year and a median observation time of 60 months.

There were 46 males and 29 females, all aged 50 years or less, 35 patients were staged III-B and the 40 remainder stage IV A/B in CR after standard MOPP or Adriamycin based chemotherapy. Relapses and remission's duration were analysed by appropriate regression analysis.

Results: The 5 year relapse rate is 30%. Univariate and multivariate analysis were performed and no factors were found among more than 20 diagnostic features of the diseases.

Attention should be paid to the development of an Harpse Zoster, and this evolution after relapse is a sensitive marker of disease relapse. Relapse rate 95% CI 2.3-11 independently of having applied consolidation therapy.

Conclusions: The results imply that failure to achieve a complete remission is the best indicator for poor prognosis in advanced Hodgkin's disease.
Second cancers in Hodgkin's disease

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*Institute for oncology and radiology of Serbia, Belgrade

The most serious consequence of curative therapy for Hodgkin's disease (HD) is the development of second cancers. In order to identify the risk of second cancers we reviewed the records of 147 patients (pts) treated between January 1970 and December 1991. The follow-up period ranged from 2 to 20 years. Disease stage at diagnosis was: I=14%, II=32%, III=42%, IV=12%. 15 years (yrs) survival rate was 65% for stage I and II while 10 yrs survival was 50%, for stages I and IV. Pts were treated initially with chemotherapy (MOPP/ABV, ABVD, MOPP-ABV) alone, with radiotherapy (RT) according to the stage, and ABVD (21) in MOPP therapy relapsed pts. Second cancers were diagnosted in 8 pts (6%), 1-13 (X7) yrs after the end of the treatment. In complete remission of HD. At HD diagnosis those pts were 17-58 (X40) yrs old; with IIB stage in 4, IIIB in 1, and IIB in 1 pts. Acute myeloblastic leukaemia was diagnosed in 2 pts: 1. FAB M4 type in pts treated only with MOPP therapy (10 cycles) after 5 yrs; 2.Fat M3 in pts treated with ABVD (3 cycles) and radiotherapy after 1 year. All other second cancers were seen in 4 pts treated with MOPP and radiotherapy, in radiotherapy - involved field: Non Hodgkin lymphoma (NHL) ventriculitis (after 9 yrs); solid cancers: pancreas (after 4 yrs) kidney (after 12 yrs), lung (after 13 yrs). Successful second cancers treatment was only in AML - M3 (continuous complete remission 2 yr) and NHL (4 yrs remission). Our results confirm as a risk factors for second cancers in HD: age, advanced clinical stage, irradiation, MOPP chemotherapy, but also show leukemic influence of ABVD+radiotherapy regimen.
LATE PULMONARY EFFECTS OF RADIOTHERAPY (RT) ALONE OR COMBINED WITH CHEMOTHERAPY (CT) IN PATIENTS WITH EARLY STAGE HODGKIN'S DISEASE (HD). Y. Bonfante, S. Viviani, L. Devizi, F. Villani, P. De Maria, M. Zanini, A. Sanzalone. Istituto Nazionale Tumori, Milan, Italy.

AIMS: To determine whether RT alone or combined with ABVD CT in patients (pts) with early stage HD induces long-lasting pulmonary damage with either clinical or subclinical evidence.

PATIENTS: We studied 36 pts with laparotomy staged IA-IIB HD and treated with subtotal nodal RT (40-44 Gy and 35 Gy to the involved or uninvolved nodal sites, respectively), and 24 pts with clinical stage IAB-IIA treated with 4 cycles of ABVD followed by mediastinal RT at the median dose of 36 Gy (range 30.6-43.2).

METHODS: Pulmonary function was serially evaluated by chest X ray, spirometric parameters, arterial blood gas analysis, alveolar-arterial PO2 difference and single breath CO transfer factor (TLCO). The tests were performed before, at the end, at 1 year after therapy and every other year during the follow-up in both treatment groups.

RESULTS: At the end of therapy there was a significant decrease of Total Lung Capacity (TLC), Vital Capacity (VC),Residual Volume (RV),Forced Expiratory Volume in 1 second (FEV1) and TLCO. After RT alone, modification of TLC, VC and RV, indicative of a pulmonary restrictive disease, occurred 1 year after completion of treatment, while the decline of TLCO was still significant 1 year later but not 2-5 years later except in 4 cases. After combined modality, on the contrary the decrease of TLC, VC, RV and TLCO, while not clinically significant, was still present 1 year from the end of therapy. In this treatment group a persistent decline of TLCO greater than 20% from baseline values was observed in only 3 pts who received respectively 36-43.2-36 Gy to the mediastinum, FEV1 recovered to normal values within 1 year in all cases.

CONCLUSIONS: These data confirm that RT induces a pulmonary restrictive dysfunction at subclinical level and show that short term ABVD produces a mild enhancement of pulmonary dysfunction that seems to be persistent in only few pts. The nature of this susceptibility remains to be clarified.

LYMPHOMA AND METACRONOUS SMALL CELL LUNG CANCER.

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Introduction. Chemotherapy (CT) and/or Radiotherapy (RT) of Hodgkin (HD) and non-Hodgkin (nHD) lymphomas allow cure in 70-80% of patients, but long term survivors who received chest radiation therapy as part of treatment program seem at high risk of developing late in-field lung cancers. Small cell lung cancer (SCLC) is the most frequent histologic type (36 to 76%).

The risk increases when smoking habits are present. Case Report. Among 103 pts with lymphoma who were given CT-RT or RT alone in our center from 1978 to 1984, 2 cases of late SCLC have been observed (2%; this rate matches other published data). Both pts were heavy smokers. They had been diagnosed as having stage III HD and, respectively, nHD lymphoma in 1980 and treated with "sandwich" CT-RT-CT. RT consisted of sub-total nodal irradiation (dose range 3450 to 3600 cGy).

Histologically proven SCLC developed 13 years later in form of disseminated and, respectively, limited disease. They were poorly responsive to CT-RT and pts died within 6 months of diagnosis.

Discussion and Conclusions. Radiation and tobacco smoke seem to be the most prominent factors in the development of secondary lung cancers in lymphoma-cured pts, although smoking is not present in all pts. Maybe that bronchial damage from radiation enhances susceptibility to carcinogenic effects of tobacco or pollution or both, possibly shortening latency. Although many variables do exist and do not allow definitive conclusions, the excess of lung carcinomas in these pts - in comparison of the normal population - and the concordance of data from various lactations make these findings very suggestive. Long term follow-up is needed in lymphoma-cured pts, particularly when tobacco smoke is present in their habits.

Relationships between sequelae reported by practitioners and by long term Hodgkin's disease survivors (HDS).


Hodgkin lymphoma in children is a medical challenge requiring cooperation between practitioners and patients. Practitioners should be aware of difficulties often reported by practitioners than patients. Late sequelae appraisal also differs between practitioners and patients. Practitioners should be aware of difficulties often reported by practitioners than patients. Late sequelae appraisal also differs between practitioners and patients. Practitioners should be aware of difficulties often reported by practitioners than patients. Late sequelae appraisal also differs between practitioners and patients. Practitioners should be aware of difficulties often reported by practitioners than patients.

Conclusion: In HDL, long term sequelae are not negligible and are slightly more often reported by patients than practitioners. Late sequelae appraisal also differs between practitioners and patients. Practitioners should be aware of difficulties often reported by practitioners than patients. Late sequelae appraisal also differs between practitioners and patients. Practitioners should be aware of difficulties often reported by practitioners than patients.

ACUTE LYMPHOBLASTIC LEUKEMIA AFTER STEM CELL MOBILISATION IN A PATIENT WITH HODGKIN'S DISEASE.


Acute lymphoblastic leukemia arising as a secondary neoplasm in Hodgkin's disease (HD) is rare. We report a patient with ALL/L3 occurring 12 years after Hodgkin's disease. In 1081 Hodgkin's disease, nodular sclerosing type, was diagnosed in a 41 year old female patient. Ann Arbor stage was III B. We administered MOPP and ABVD and a complete remission was achieved. In 1984 patient relapsed three times in mediastinum and received several regimen and radiation. In 1994, during complete remission, a stem cell pheresis after induction with cyclophosphamide and G-CSF was done. Harvested CD 34+ cells were few. In 1996 patient was readmitted with dyspnoea, fatigue and hematuria. In peripheral blood count we found leukocytosis of 21,000/ml, anemia and thrombocytopenia and serum LDH was 11,214 U/l. Bone marrow biopsy and immunophenotyping indicated typical ALL/L3. (H.LA-DR, m-tum and CD19 positive). Cytogenetic analysis showed the typical stem line aberration t(1;14). We administered HD-ARA-C, but in spite of intensive support patient died on sepsis, pneumonia and renal failure. As both Hodgkin's disease and ALL/L3 are EBV associated we postulated that EBV has induced the leukemia. In 1997 patient died on sepsis, pneumonia and renal failure. As both Hodgkin's disease and ALL/L3 are EBV associated we postulated that EBV has induced the leukemia.
A CASE OF TRACHEO-OSOPHAGEAL FISTULA AS A COMPLICATION OF PULMONARY HODGKIN'S DISEASE.

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We report a case of pulmonary Hodgkin's disease complicated by tracheo-osophageal fistula which was successfully managed conservatively with chemotherapy. Primary lymphoma in the oesophagus is rare and the occurrence of tracheo-osophageal fistula (T.O.F.) is even rarer. The development of a T.O.F. is known to be a very poor prognostic factor. In patients with Hodgkin's lymphoma, T.O.F. usually develops as the result of widespread active disease from cervical and mediastinal lymphadenopathy or the stomach and is rarely the primary. A 49 year old man who had a past history of an achalasia cardia presented with Stage IIIB Nodal scleroma Hodgkin's disease with cavitating pulmonary lesions. He received combination chemotherapy and achieved a partial remission. He then presented with cough on swallowing and a chest X-ray revealed a new right upper lobe shadowing and a barium swallow subsequently confirmed a tracheo-osophageal fistula from the posterior oesophagus to the right carina. He was treated conservatively by inserting a gastrostomy tube for feeding purposes and further chemotherapy which resulted in a successful outcome with a reduction of his pulmonary Hodgkin's disease and complete healing of the tracheo-osophageal fistula. A barium swallow during the same period revealed extensive stenosis of the carina for which a laparoscopic myotomy was carried out. The gastrostomy tube was subsequently removed and normal eating habits returned. He was subsequently given high dose chemotherapy with stem cell rescue and has remained in complete remission since. As far as we are aware T.O.F. has not been reported in the context of normal habitus. He was subsequently given high dose chemotherapy with stem cell rescue and has remained in complete remission since. As far as we are aware T.O.F. has not been reported in the context of normal habitus. He was subsequently given high dose chemotherapy with stem cell rescue and has remained in complete remission since.

Late complications of mantle radiotherapy for Hodgkin's disease.

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The British National Lymphoma Investigation (BNLI) database for Hodgkin's disease of patients treated with radiotherapy at Mount Vernon Hospital between January 1970 and December 1985 has been searched for reported complications of radiotherapy in 141 sequentially registered patients. A total of 35 specific complications in 32 patients have been found. These comprise lung 15 (fibrosis 10, multiple infections 5), cardiac 6 (cardiac failure 3), myocardial infarction 2, pericarditis 1, laryngeal 4, serous meningitis 4, hypo-thymalid 2, and one each of severe skin fibrosis, em oedema, oesophageal stricture and jejunal ulceration. Thirteen of the 32 patients have died, treatment related events may have contributed to death in 8 of these. This however includes 2 deaths from ischaemic heart disease and 2 from excursions of the bronchus which may have been incidental events leaving 4 patients in whom death was unequivocally related to complications of treatment, a treatment related mortality rate of 2.1%. The median age at time of diagnosis and primary treatment was 36 years (range 15-71) and the median time of onset of complications from treatment was 104.5 months (range 8-324 months). Median time to cardiac complications was 118 months (range 55-1194), and bone complications was 90.5 months (range 8-246 months) with two clear patients emerging of early lung complications seen in 6 patients between 8 and 20 months follow by late complications in the other 9 patients emerging between 89 and 246 months. The second tumours were seen at 93 months (es oesophagus), 117 months (renal cell cancer), 129 months (non small cell lung cancer) and 324 months (senoidal giant cell). These tumours were all within the radiation field. Treatment in this era was predominantly using a cobalt beam with only 5 patients treated with SMV linear accelerator and 5 patients with VMV linear accelerator. Treatment technique was by either direct field alone (9 patients) or a direct field with posterior mediastinal boost delivered once or twice weekly (18 patients). Only 4 patients were treated with daily opposed AP fields. Of the 24 patients treated with a cobalt beam in a single course of treatment to the mantle area or neck was delivered. The midplane dose defined in these patients was between 3000 and 4500 Gy with 13 patients receiving 4000 Gy. The low beam energy and treatment technique however resulted in much higher acute side effects when compared to the general population, deriving observed/expected ratios for the different clinico-therapeutic subgroups of this series have been analyzed with univariate and multivariate analysis (Cox model). The baseline characteristics of the patients included in this analysis are shown in Table 1. The incidence of radiation related mortality was 2.1%.

20 YEARS EXPERIENCE WITH HODGKIN'S DISEASE (HD) AT THE UNIVERSITY OF FLORENCE: THE REMAINING CHALLENGE AFTER A "SUCCESS STORY"


Purpose: During the last twenty to thirty years remarkable gains in survival of HD patients (pts) have been achieved. The two main goals actually pursued by all the major Centers are a reduction of the toxicity of the treatment for the majority of the pts with better prognostics and the adoption of a more aggressive clinical behaviour in the minority with a "high risk" of relapse and/or death. We therefore reanalyzed the series of the Radiotherapy (RT) and Hematology (HE) Departments of the Florence University (UF), that have worked together in the management of HD in the last two decades, aiming at a better definition of the prognostic value of the different clinico-therapeutic factors and to evaluate treatment results in the different subsets of pts.

Materials and methods: From 1960 to 1991, 1531 pts have been treated with radical sim. Half of them have been submitted to staging laparoscopy with splenectomy. The main features of the series are as follows: Clinical Stage (CS) I, 13%; II, 48%; III, 30%; IV, 9%; General symptoms: A, 68%; B, 32%; Histology: LP,12%; NS,43%; MC,40%; LD,3%; Treatment as presentation: RT alone, 52% Chemotherapy alone, 27%; Combined modality, 21%. Differences in survival rates among the different subsets of pts or according to the treatment given have been analyzed with univariate- and multivariate analysis (Cox model); the same was done for the incidence of the main types of jurassic damage. Results: Actuarial HD disease specific survival for the whole series ranged 88% (CS I-III) to 41% (CS IV pts). A detailed analysis of survival and toxicity results in the different subsets of pts will be presented.

SECOND MALIGNANT NEOPLASMS AFTER HODGKIN'S DISEASE (HD): AN ANALYSIS OF 1531 PATIENTS (PTS) TREATED IN FLORENCE (1960-1991)


Purpose: To define the risk of having a second malignant neoplasm (ST) in different subsets of HD patients, therefore possibly identifying clinico-therapeutic factors linked with an increased second tumor probability.

Methods and materials: Cumulative probability of having a ST has been calculated for the different clinical and therapeutic subgroups of a population of 1531 patients consecutively treated (1960-1991) for HD at the Florence Radiotherapy and Hematology Departments. Clinical stages (CS) at diagnosis were distributed as follows: CS I, 13%; II, 48%; III, 30%; IV, 9%. Initial treatment consisted of radiation alone (52%), combined modality treatment (21%), chemotherapy alone (27%). Incidence data in the different clinico-therapeutic subgroups of this series have been compared with multivariate analysis (Cox model). A comparison has been also made with the general population, deriving observed/expected ratios for the different tumor types. For selected tumor types, a "tested" case-control study is ongoing.

Results: An increased ST risk has been observed in patients older at HD diagnosis. The same trend was observed for second solid tumors (STT). However, the incidence of ST rates strikingly after very long follow up intervals, so that it is desirable to follow up indefinitely the cohorts of pts younger at HD diagnosis. Acute leukemia was more frequent in patients initially given chemotherapy, alone or associated with radiotherapy, while the relationships between SST occurrence and the treatment given are less evident.

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HYPOTHYROIDISM AFTER HODGKIN'S DISEASE. A new pathogenic hypothesis from a study of 51 patients treated by 3 courses of the ABVD-MP regimen and a 40 Gy radiotherapy.

V.P. Shust and A.B. Markochev, Central Research Institute of Roentgenology and Radiology, St. Petersburg, Russia.

The basic thesis of the study are evaluation of antitumor cytostatic treatment of patients as the cancerogenic factor and search for the signs of susceptibility of Hodgkin's disease patients to *tumor disease?These signs can be regarded as the presence of malignant tumors incose relatives - first degree of relationship on relations. The second neoplasms were detected in 21 patients from 466, treated in Institute in 1968-1983(4.5%); IT males, 10 females. At the time of the second neoplasms detection the age was 52,3+2,6 years. The interval between the beginning of the treatment and detection of the second tumor was 7,8+0,9 years. All the patients were subjected to irradiation treatment. Only in ten the second tumor developed in the irradiation field. Chemotherapy was used in 16 out of 27 patients. Susceptibility of H.D. patients to the *tumor disease? was evaluated by calculation of the cumulative observed risk of development of the second malignant tumors. During the II-th year after the beginning of treatment cumulative observed risk(COR) for all 466 patients with H.D. was 500X10^-4. In 428 H.D. patients with non-compromised heredity the (2nd malignant tumor in 18 patients)COR was 470X10^-4. In 7 patients with H.D. with 1-st degree relatives who had H.D., COR was 590X10^-4. This figure is statistically greater than for patients with non-compromised heredity.(p<0,05). We believe, these data support the hypothesis of multifactor nature of the second malignant tumor in H.D. patients' disease.

5. Hodgkin's Disease

B7 IMMUNOTOXINS AS POTENTIAL THERAPY FOR HODGKIN'S DISEASE.


Hodgkin-Reed-Sternberg (HRS) cells are considered to be the malignant cells in Hodgkin's Disease (HD) and certainly are producers of cytokines, which contribute to the diseases symptoms. Anti-tumor immune responses include CD30, CD40, IL-2R and B7, which may be used as targets for immunotherapy. B7-1 and B7-2 mAbs showed in immunohistochemistry strong staining in Hodgkin's disease tumors, HRS and dendritic cells (DC). No staining with a series of other tissues was found. No toxicity was associated with the treatment of the patients with B7-1 and B7-2 immunotoxins (IT) which were constructed with gelonin as toxin. They showed cytotoxicity to B-cells and HRS cell lines expressing B7-1 and B7-2. Anti-tumor responses were found in patients treated with either B7-1 or B7-2. Both B7-1 and B7-2 were effective in treatment of patients with HD.

About factors that have an influence on the origin of the second neoplasms of patients with Hodgkin's disease

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A Case of Hodgkin's Disease with Idiopathic Intrahepatic Cholestasis and "Vanishing Bile Duct Syndrome".

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A small percentage of patients with Hodgkin's disease in the absence of lymphomatous liver infiltration develop a distinct syndrome of idiopathic intrahepatic cholestasis. The liver disease is often progressive and may be fatal, even following eradication of the Hodgkin's disease. A single report has suggested an association with loss of bile ducts. A previously well 42-y.o. woman presented with lethargy and neck adenopathy. Biopsy revealed nodular sclerosing Hodgkin's disease. Clinical staging was IIIA. She took no medication, but had abnormal liver enzymes: ALT 114 IU/L (<50), yGT 680 (<35), alkaline phosphatase 793 (<120) and bilirubin 15 μM (<17). Although CT and gallium imaging of the liver was normal, lymphomatous infiltration was suspected and the patient was treated with alternating MOPP-ABVD. Despite complete resolution of her disease after 6 cycles, the liver enzymes remained abnormal. Needle biopsy of the liver revealed chronic intrahepatic cholestasis and features of "vanishing bile duct syndrome". There was no histologic or serologic evidence of active infection with hepatitis A, B, or C, EBV or CMV. The patient relapsed with biopsy-proven isolated peripheral nodal disease 3 months after completing chemotherapy and proceeded to autologous stem-cell transplantation following BEAM chemotherapy. Prostaglandin-E, was given as vaso-occlusive disease prophylaxis and the bilirubin level peaked at 76 μM. Despite achieving ongoing CR now 18 months post-autograft, the liver enzymes remain abnormal but stable; ALT 243, yGT 533, alkaline phosphatase 300 and bilirubin 19. This case suggests that, at least in some instances, "vanishing bile duct syndrome" may be the pathology underlying the idiopathic intrahepatic cholestasis of Hodgkin's disease. The mechanism of this bile-duct loss remains uncertain but may be immunologically mediated.