4. Paediatric Lymphomas

CHROMOSOME ABNORMALITIES IN ADVANCED LYMPHOMATOID Lymphoma (LBL) in CHILDREN AND ADOLESCENTS MAY CORRELATE WITH PROGNOSIS: A REPORT FROM CHILDREN'S CANCER GROUP (CCG) STUDY CCG-E-08.

Children's Cancer Group, Arcadia, California, USA.

Introduction: CCG has reported that specific chromosome abnormalities are associated with prognosis in childhood pre-Acute lymphoblastic leukemia (Heerema et al. Blood 94:4036, 1999), but few cytogenetic studies have been performed in childhood LBL.

Methods: The protocol CCG-E-08 "Etiologic Study of NHL in Childhood" enrolled 13 patients with LBL who had cytogenetic analysis and were entered into a treatment protocol for advanced stage LBL (CCG-502, total patients=281). Pathology and cytogenetic materials from initial diagnosis underwent central review.

Results: Demographics: age range 6-13 years (median 9 years); male/female ratio 12:1. Institution immunophenotyping was reported in 9 cases: T-cell 8, B-cell 1. All 13 patients had advanced stage LBL (marrow and CNS negative), including 10 with mediastinal mass. Relapse occurred in 6 patients: 3 in the 1st year, 2 in the 2nd year, and 1 in the 3rd year (EFS 54% ± 14%, follow-up range 7-12.7 years, median 10.8 years). All patients with relapse died (5/6 with disease). Chromosome abnormalities were identified in 11 cases (85%). Chromosome translocations involving the T-Cell Receptor (TCR) αβ locus at 14q11.2 were present in 4 cases (35%), and included t(1;14)(p32;q11.2) (BCL1/ALL gene), t(8;14)(q24;q14.2) (MYC gene), t(1;14)(p11;q11.2) (LMO1 gene), and t(14;20)(q11.2,p13). There were no cases with rearrangements of the TCR β or γ loci or 7q32 or 7q35, respectively. Of the 6 patients who relapsed, 3 had the t(1;14), t(8;14), t(11;14), or t(14;14). Another case with relapse had a (8;17)(q32;q21) which may involve the TANI gene at 9q43. The patients without relapse did not have translocations involving 1p32, 2q24, 9q34, or 11p13. One patient with a precancerous B-cell LBL presented without a mediastinal mass and relapsed with the 1st year; the lymphoma was hyperdiploid without an abnormality at 14q11.2.

Conclusions: Pediatric advanced LBL have a high frequency of chromosome abnormalities that often involve translocations of the TCR αβ locus at 14q11.2. Translocations involving 1p32, 2q24, 9q34, and 11p13 were associated with poor prognosis. This pilot data suggests that chromosome translocations of the TCR locus and T-Cell oncogenes may confer prognosis and potentially alter treatment strategies in childhood advanced LBL. Further study in large numbers of patients including FISH, CGH, RT-PCR, and arrays may provide additional pertinent information.

TWO DECADES OF PROGRESS IN THE TREATMENT OF B-CELL ACUTE LYMPHOMATOID LEUKEMIA (B-ALL): THE PEDIATRIC ONCOLOGY GROUP EXPERIENCE 1979-1999

T. Griffin, M. Schwartz, P. Bowman, M. Sullivan, J. Kersey, and S. Murphy for the Pediatric Oncology Group

Introduction: In 1982, treatment (Rx) was instituted in the POG which was specifically tailored to the unique features of B-ALL.

Methods: Three retrospective studies were conducted. POG 8106 (Sullivan, Leukemia, 1990) employed a COMP regimen of 1 yr duration. Subsequent studies employed a modification of Total Therapy B (Murphy, JCO, 1986), which utilized fractionated cyclophosphamide, vincristine, and dexamethasone with alternating courses of early IV infusions of methotrexate and cytosine. POG 8617 (Bowman, JCO, 1996) used a dose-intensified cytosine therapy and modified for either 6 or 8 courses of Rx over approximately 5-6 mos. POG 8117 compared two different schedules of high-dose cytosine with or without the inclusion of a VP-16/ifosfamide intensification course following remission induction; Rx duration was 5 mos. All protocols included intensive intrathecal (IT) Rx delivered by lumbar puncture. No CNS radiation was employed. The routine use of G-CSF support was added during POG 8617, in 1991. Only a small number of pts on 9117 received recombinant human erythropoiesis.

Results: A great majority of males was seen in all studies, as expected. The results for specific protocols are presented below:

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Years</th>
<th># Pts</th>
<th>CRIS</th>
<th>EFS%</th>
<th>CNS+</th>
<th>CNS-EFS%</th>
</tr>
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<tbody>
<tr>
<td>8106</td>
<td>1982-86</td>
<td>20</td>
<td>85%</td>
<td>20±0</td>
<td>10</td>
<td>0%</td>
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<tr>
<td>8617</td>
<td>1986-92</td>
<td>74</td>
<td>89%</td>
<td>65±7%</td>
<td>19</td>
<td>53-116%</td>
</tr>
<tr>
<td>9117</td>
<td>1991-99</td>
<td>82</td>
<td>94%</td>
<td>79±6%</td>
<td>28</td>
<td>79-97%</td>
</tr>
</tbody>
</table>

The most frequent site of failure was the marrow followed by CNS. Without the use of urate oxidase, metabolic complications and renal insufficiency during induction were common. Hematologic and infectious toxicities were frequent but usually manageable. Neurologic toxicity was problematic in 8617 but lessened with reduction of intensity of IT therapy.

Conclusions: Results from successive Rx protocols for B-ALL in POG represent a great success story for pediatric oncology. Future directions of investigation include better supportive management, identification and more effective Rx for pts at highest risk of failure, and inclusion of new agents to improve EFS or diminish chemo Rx.

TREATMENT RESULTS IN CHILDHOOD B-CELL NEOPLASMS, REPORT OF THE POLISH PEDIATRIC LEUKEMIA LYMPHOMA STUDY GROUP (PPLLeS).


Departments of Children Hematology, Oncology, Pathology, Medical Schools Wrocław, Poznań, Bydgoszcz, Gdańsk, Kraków, Lublin, Poznań, Wrocław, Zabrze, Poland.

Introduction: The efficacy of a LMB-89 protocol for children with B-NHL/Burkitt-like, large cell and L3 leukemia has been investigated. The patients (pts) were treated in 11 oncological centers of PLLLeS during 1993-2001 yrs. In this study, 139 pts were analyzed. Medical condition of children was by 7 age and medium time was observation of 52 months.

Methods: The diagnosis was based on histomorphological investigation and supplemented with immunohematological. The staging system of S. Murphy was used for prognostic stratification. Treatment intensity was adapted to 3 risk group acc. to LMB-85.

Results: The majority pts were in advanced st. of admission: 57% in st. III, 23% in st. IV and only 5% in st. I and 15% in st. II. Primary sites were: abdomen in 50%, peripheral lymph nodes in 17%, head-neck in 21%, elsewhere in 12%. Five (5%) pts were treated in gr. A, 79% in gr. B, 16% in gr. C. Complete remission was achieved in 89% pts, 94% with LDL > 500 UL and 84% with LDL > 500 UL. There were 6 (6.9%) non responder pts (all with extensive tumor, st. III and high LDL), 3.4% early death (tumor lysis syndrome: circulatory insufficiency), 2.2% deaths after CR due to therapy toxicity and 1.4% deaths in CR due to infection. Twelve pts relapsed (13%), EFS is 0.73 for all pts, 0.83 in group A, 0.68 in group B and 0.56 in group C; 0.1 st. I+III, 0.81 st. III and 0.55 st. IV with a median follow up of 52 months. The EFS of pts with LDL > 500 UL 0.87 for LDL > 500 UL. There were 6 (6.9%) non responder pts (all with extensive tumor, st. III and high LDL), 3.4% early death (tumor lysis syndrome: circulatory insufficiency), 2.2% deaths after CR due to therapy toxicity and 1.4% deaths in CR due to infection. Twelve pts relapsed (13%), EFS is 0.73 for all pts, 0.83 in group A, 0.68 in group B and 0.56 in group C; 0.1 st. I+III, 0.81 st. III and 0.55 st. IV with a median follow up of 52 months. The EFS of pts with LDL > 500 UL 0.87 for LDL > 500 UL. The most frequent site of failure was the marrow followed by CNS. Without the use of urate oxidase, metabolic complications and renal insufficiency during induction were common. Hematologic and infectious toxicities were frequent but usually manageable. Neurologic toxicity was problematic in 8617 but lessened with reduction of intensity of IT therapy.

Conclusions: Results from successive Rx protocols for B-ALL in POG represent a great success story for pediatric oncology. Future directions of investigation include better supportive management, identification and more effective Rx for pts at highest risk of failure, and inclusion of new agents to improve EFS or diminish chemo Rx.
DETECTION OF MINIMAL RESIDUAL DISEASE IN CHILDHOOD BURKITT'S LYMPHOMAS AND B-CELL ALL. K. Busch, A. Borkhardt, J. Harbott and A. Reiter. Oncogenetic Laboratory, Children's Univ. Hospital, Feulgensstr. 12, D-35385 Giessen, Germany.

The t(8;14)(q24;q32), involving MYC gene (8q24) and the immunoglobulin heavy chain (IgH) locus (14q32), represents about 75% of all translocations in childhood Burkitt's lymphomas (BL) and B-cell ALL. Due to the great variability of the breakpoint region, a standard polymerase chain reaction (PCR) assay is not sufficient for the detection of this chromosomal translocation. The recently improved long-distance (LD) PCR for the detection of t(8;14)(q24;q32) allows to identify the specific breakpoint region within the MYC gene and the IgH locus. The combination in different reactions of one primer specific for MYC exon II and four primers for the IgH locus, localized within the joining region (JH) and the constant regions (Cu. Cy and Co), reveals the specific breakpoint region. Our investigations of Burkitt's lymphoma cell lines and several childhood BL or B-ALL, positive for t(8;14)(q24;q32), showed a product ranging in size from 1 to 10 kb. The LD-PCR, however, reached a sensitivity of 10^3 only, which is not sufficient for detection of minimal residual disease. Therefore, we established a more sensitive nested PCR with a specific primer combination for each patient based on sequence analysis of the variant breakpoint regions. Thereby, two primers were specific for the MYC-gene close to the MYC/IgH breakpoint and one primer is located in the IgH locus, whereas another one overlapped the breakpoint of each specific breakpoint region. To establish the specification, we investigated the Burkitt lymphoma cell line CA-46 and several pediatric BL or B-ALL using their specific primer combination for the nested PCR in comparison with lymphoma cell lines and pediatric leukaemia where are negative for t(8;14)(q24;q32). Using this breakpoint specific nested PCR, we could detect the translocation in 1 out of 10^6 hematopoietic cells lacking this translocation. In conclusion, we represent a combination of LD- and nested PCR method as a specific and sensitive tool for the evaluation of minimal residual disease in patients affected by t(8;14)(q24;q32)-positive lymphomas.


Introduction: ALCL is a subtype of T cell/natural killer cell lymphoma with heterogeneous clinical features and morphologic/imunophenotypic overlap with other large cell lymphomas, making accurate diagnosis difficult.

Rearrangement of the ALK gene is common. Methods: 20 ALCL patients were identified using the criteria of T or null cell phenotype, and expression of CD30, ALK and/or EMA proteins. Cytogenetics, FISH and/or RT-PCR were used to detect ALK gene rearrangements (GR) in cultured tumor tissue or preserved sections. Results: FISH detected ALK GR in 15 patients. Cytogenetics and PCR each detected another. Of these cases, a t(2:5) or NPMALK fusion was confirmed in 6. Three were not studied by FISH or PCR. Four patients had ALK-variant GR: a 8q22(q22:p23), a t(2;19)(p23;p13.3), an inv(2)(p23q35), and an abnormal karyotype without a 2p23 abnormality. Conclusions: Novel ALK GR may be under-detected, requiring FISH and cytogenetics to elucidate them. The partner gene for the insertion 8q2 is not known, and this is a newly described ALK GR. We reported that the t(2;19) results in a novel ALK/TFM4 fusion gene (Meche et al., Blood 98, 2001). The inv(2) is most likely an ATIC/ALK fusion. It is critical to verify ALK GR as part of ALCL diagnosis, concomitant with immunophenotype and ALK and EMA expression. ALK genetic studies contribute to the discovery of novel mutations in ALCL.

CHILDHOOD ANAPLASTIC LARGE CELL LYMPHOMA WITH CNS INVOLVEMENT. L. Brugière, M. Dubret, A. Babin-Boilette, G. Deloix, R. Stephane, C. Patte, C. Bayle, O. Hartmann, I. Institut Gustave Roussy - Villejuif, J. Hôpital Haupteipenne - Strasbourg, J. Hôpital Purpan - Toulouse, C. Hôpital Dieu - Clermont Ferrand France. Objectives: to study the outcome of children with anaplastic large cell lymphoma (ALCL) involving CNS at diagnosis or at relapse.

Patients and methods: Among more than 100 patients registered in the French data base for childhood ALCL between 1975 and 1999, only eight cases were diagnosed with a CNS involvement at diagnosis (4 pts) or at relapse (4 pts). We retrospectively reviewed clinical, pathologic and radiologic data from these children.

Results: There were 4 boys and 4 girls aged 5 years to 17 years (median 10 y). Four patients were diagnosed with primary CNS ALCL revealed by a intracranial mass in 2 patients and the presence of tumor cells in CSF in two patients. In one patient CSF involvement was isolated and diagnosed by the presence of t(2;5) in the CSF. The other three children also had nodal or visceral involvement by the lymphoma. All four children were treated with LBMB9 group C protocol with 18 to 24 Gy cranial radiotherapy. They all achieved complete remission. Three are alive disease free with 2, 6 and 9 years follow-up and one who experienced a bone marrow relapse 9 months after diagnosis, is still on therapy. ALCL involvement occurred at relapse in 4 children. It was the first relapse for 3 patients and the second relapse for the last one. First line treatment had been COPAL in 2 patients, JBMS1 for one patient and SIOP MMT 89 protocol for the last patient who had been misdiagnosed with a rhabdomyosarcoma. CNS relapse was isolated in all 4 children. It was revealed by a cerebral mass in 3 children and by the presence of cells in CSF in one patient. One child died before any specific treatment for the CNS relapse. The other three children received a combination of high dose etoposide and high dose cytarabine with cranial radiotherapy. Two are alive disease free with 10 and 11 year follow-up and the third one deceased after a third relapse. Overall, 5 patients are alive disease free with 2 to 11 years (median 9 years) and 2 patients died.

Conclusions: CNS involvement in ALCL is rare (<1%). Treatment combining high dose methotrexate, high dose cytarabine and cranial irradiation according to the LBMB9 protocol is highly efficient for these patients.


ALCL shows a broad spectrum of morphologic appearances and in addition to its classic form several variants have been described. The differential diagnosis with Hodgkin's disease and other T-cell lymphomas may be difficult, particularly in ALK negative cases. The purpose of this study was to better define the immunophenotype of a representative series of pediatric ALCL (36 cases) including 20 classic cases, 4 pure small cell or lymphohistiocytic variants, 6 mixed cases and 6 other miscellaneous variants. All the cases had a T or null phenotype and expressed the following markers on formalin-fixed, paraffin-embedded tissue: CD30 (97%), CD2 (83%), CD5 (12%), CD4 (21%), CD8 (15%), CD15 (5%), CD25 (4%) and CD70 (5%). In 5 cases, CD30 was also positive. CD1a (10%), CD20 (10%), CD43 (67%), CD45RO (60%), CD56 (10%) and CD57 (0%). ALK1 (80%) and ALK2 (10%). EMA (88%). Cytotoxic proteins: Tial (84%); granzyme (78%). Clusterin (91%), CD8 (38%). Fascin (34%). The high percentage of ALK1 positive cases in our series is related to the pediatric age of the studied population. In addition to ALK1 other useful diagnostic markers include cytochrome molecules and clusterin. Fascin positivity is seen in about 1/3 of the cases but the intensity of the immunoreactivity is usually lower than in HD; on the contrary CD30 is commonly expressed in classic HD and only exceptionally in ALCL.
ANALYSIS OF A LARGE COHORT OF CHILDHOOD ANAPLASTIC LARGE CELL LYMPHOMA (ALCL) BY IMMUNOHISTOLOGY AND FISH: DIFFERENTIAL ALK GENE REARRANGEMENT AND EXPRESSION

Introduction: ALCLs often have a cytogenetic abnormality involving the ALK region on chromosome 2p23; however, the incidence and breakpoints of ALK translocations in a large cohort of childhood ALCL treated on a uniform treatment protocol are relatively unknown. We analyzed 46 cases of childhood ALCL treated on CCG-5941.

Methods: FISH analysis was performed on paraffin-embedded tissue sections by 46 histologically centrally reviewed and characterized cases of childhood ALCL (39 T-cell, 5 null phenotype and two unknown). All cases were CDO2(+) with typical morphologic features. ALK-1 IHC was performed on 42/45 cases. FISH analysis was performed using a NPM/ALK translocation probe to detect the t(2;5)(p23;q35). Those cases that failed to demonstrate this translocation hybridized with a dual color ALK breakapart probe that can detect alternative rearrangements involving the ALK gene locus in addition to the t(2;5). Cases were analyzed to determine the number and pattern of probe signals to provide insight into the molecular events associated with each tumor.

Results: Of the 38 cases analyzable by IHC, 25 were positive with the NPM/ALK FISH probes, indicating the presence of a t(2;5)(p23;q35). 5 cases that were negative for NPM/ALK were positive with the ALK probe, suggesting an alternative ALK translocation and 8 cases did not show a detectable ALK translocation. ALK-1 IHC was positive in 39/42 cases (93%). The 3 cases that were negative for ALK-1 by IHC included 3 cases with no detectable ALK rearrangement by FISH. 1 case that was positive with the NPM/ALK probe and 1 case that was negative for NPM/ALK but positive with the ALK probe. The 25 cases that were positive with the NPM/ALK probe showed a nuclear staining pattern associated with the (t;2;5), whereas those cases that were positive with ALK probe included 2 cases with nuclear and cytoplasmic ALK-1 staining, 2 cases with nuclear staining alone and 1 case that did not stain. All 7 cases that failed to demonstrate an ALK rearrangement by FISH showed nuclear ALK-1 staining.

Conclusions: Of the 38 ALK FISH positive cases, 84% were positive for t(2;5) (p23;q35) and 16% were positive for an ALK rearrangement other than t(2;5). Similarly, ALK-1 IHC was positive in 93% of the cases tested. Use of a combination of an ALK-1 IHC and FISH identified ALK translocations and/or expression in 98% (45/46) of cases. The clinical implications of differential ALK gene rearrangement in childhood ALCL will be analyzed in the near future.

FEASIBILITY OF A PEDIATRIC PROTOCOL IN YOUNG ADULTS WITH HODGKIN DISEASE: TOXICITY AND RESULTS
M. Mott1, G. Kandil1, H. Tuchler1, M. Fillits1, K. Dieckmann1, R. Potter1, E. Fitterman1

The german pediatric protocol OPPA/COPP involved radiotherapy showed excellent results in pediatric patients. We treated 37 adult patients with a median age of 30 years (range 16-39 years) as follows: localized stages IAB, without risk factors (n=11) received 2 cycles OPPA (Adriamycin 40 mg/m², Vincristin 1.5 mg/m², Procarbazine 100 mg/m²) + Prednimustine 60 mg/m² + involved field RT 35 Gy. Intermediate stage 1Ib with risk factors and stage 3 without risk factors (n=15) received 2 OPPA, 2 COPP (Cyclophosphamid 500 mg/m², Vincristin 1.5 mg/m², Procarbazine 100 mg/m², Prednimustine 40 mg/m²) + involved field RT 35 Gy. Advanced stages 2b and 3A with risk factors 2B AAB received 2OPPA,2COPP cell-mobilization-2COPP and involved field RT 250 Gy. Stem cell mobilization in the high risk group was not part of the original pediatric protocol. Remission status post therapy was complete CR/Cru in localized stages, 100% CR/Cru in intermediate stages and 81,8% CR/Cru, 18,2% PD in advanced stages. After a median observation time of 40 months 4 relapses occurred, 2 pat. had progressive disease, 2 pat. died of Hodgkin disease, 1 pat. got into remission with conventional chemotherapy and 3 patients again achieved remission with autologous stem cell transplantation. Neutropenia grade 3/4 occurred in 5-10% but was only transient. Haematotoxicity grade 3/4 occurred in 2-37%. We never had life threatening infections or therapy related deaths. We had no case of second malignancy up to now. Conclusion: OPPA/COPP involved field RT is a safe and effective protocol for young adults. Early stem mobilisation as a part of first line therapy for high risk patients was a good chance for relapsing or progressive patients to achieve complete remission again.

VINCBLASTINE AS SALVAGE TREATMENT FOR REFRACTORY OR RELAPSED ANAPLASTIC LARGE CELL LYMPHOMA (ALCL): A REPORT FROM THE FRENCH SOCIETY OF PEDIATRIC ONCOLOGY
L. Brugères1, H. Pascopel1, MD Tabone1, MC De La Die1, C. Bergeron2, K. Perel1, O. Hartmann1, Institut Gustave Roussy – Villejuif1, Institut Curie Paris 2, Hopital Trousseau – Paris, 4 Centric Léon Béard – Lyon, 5 Hopital d’Enfants – Bordeaux – France

Objectives: to study the outcome of children treated by weekly vincristine for a relapsed ALCL.

Patients and methods: 27 children were treated with weekly vincristine for a refractory or relapsed ALCL. Their first line treatment had been COPAD (4 pts), SFOP HDM9 protocol (2 pts), SFOP HDM9 protocol (13 pts), SFOP HDM7 protocol (5 pts), another protocol for 3 pts. Status of the patients at the beginning of vincristine was resistant disease (2 pts), first relapse (9 pts), second relapse (11 pts), third relapse (3 pts). 5 pts relapsed (1 pt), 5 pts relapsed (1 pt), 10 patients had had a high dose chemotherapy with ABMT or PSCBMT as a consolidation therapy for a previous relapse.

Vincristine dose was given weekly at a dose of 6ng/m² for 6 to 24 months (median 12 months). About half of the patients also received steroids for 2 to 2 months.

Results: Response was evaluable in 25 pts: 19 patients achieved CR and 6 patients experienced a progressive disease. Among the non responding patients, 5 died and the 6th was rescued by oral VP16 and is alive disease free with 7 years follow-up (FU). Among the 21 non progressing patients, 3 were treated with high dose chemotherapy and PSCBMT after CR, 2 of them died and one is alive disease free with 7 years FU. The other 18 patients were given Vincristine for 9 to 16 months, 6 are still in continuous complete remission with a median of 6 years FU since the beginning of vincristine and 12 relapsed 2 to 48 months after the beginning of vincristine (median 12 months). Two of them died, 10 are alive disease free, 9 still on therapy.

Overall, among these very high risk patients, 9 died and 18 alive disease-free including 8 patients still on therapy.

Conclusion: Vincristine is highly efficient in inducing CR in relapsed or refractory ALCL. The question of its efficacy as a maintenance in front line treatment of high risk ALCL is raised in the on-going European ACLL97 randomised trial.

IDENTIFICATION OF PATIENT SPECIFIC PRIMERS (PSPs) of IgH and TCR-y REGIONS by NESTED PCR in CDR3 POSITIVE HODGKIN DISEASE: A CHILDREN'S CANCER GROUP REPORT (CCG)
B. Shair, E. Mori, S. Perkins, M. Lones, K. Kelly, M. Weiner, R. Spoto, M. S. Canio. University of Hawaii, Honolulu, HI, Children's Hospital of New York, Columbia University, NY, NY, University of Utah, Salt Lake City, Utah, Children's Hospital of Orange County, Orange, CA, Children's Cancer Group, Arcadia, CA, USA

Introduction: Amplification of immunoglobulin heavy chain (IGH) and T-cell receptor (TCR) regions is frequently successful in monitoring minimal residual disease (MRD) for the T-cell malignancies, particularly in identifying patient-specific primers (PSPs). In cases where CD20(+) cells are present in classic Hodgkin disease (HD) specimens, PSPs from IGH or TCR region could potentially be used to follow MRD during treatment. We have previously identified 13% and 0% of children with HD that express CD20 and CD3, respectively (Lones et al, Leuk & Lymph 42(2):197a, 2001). Therefore an analysis of specimens from cases of pediatric HD was undertaken.

Methods: Undiluted slides were obtained from each of 12 diagnostic specimens of pediatric HD treated on CCG-59704, which were previously characterized independent to this study. Adequate DNA was obtained from 10/12 cases. Amplification reactions were set up using VDJ and TCRy primers (Sabanow et al, Ped Res 49:208A, 2001) for each specimen using nested PCR parameters. Positive controls of previously characterized B- and T-cell non-Hodgkin lymphoma (NHL) specimens were used for each run. Amplified products were cloned and sequenced. Results: Six CD20(+) and 6 CD20(-) HD specimens that were centrally immunophenotyped were obtained. Amplified bands from the positive controls were sequenced and confirmed. Only one CD20(+) HD case showed amplification of the IgH region (negative for TCRy) while the other CD20(+) and CD20(-) cases were negative for IGH or TCRy amplification.

Conclusions: CD20(+) NHL cases are usually of B-cell origin, which have been utilized to amplify the IGH region in and some cases, TCRy region. Our study is the first to look at CD20(+) HD cases to see if a similar pattern can be detected, which would have provided a mechanism to design PSPs to monitor MRD. From the 6 CD20(+) specimens examined, only one amplified the IgH region. This suggested the limited use of this approach to measure and follow MRD in CD20(+) HD. However, a larger number of specimens will be examined to confirm this observation.
Ewa Gorczyńska1, Dominik Turkiewicz1, Jacek Toporowski1, Krzysztof Kalwak1, Alicja Chybicka1, Jerzy Kowalczyk1, Beata Wójcik2
Departments of Pediatric Oncology/Hematology in Wroclaw1 and Lublin2

Since May 1995 to November 2001 38 children aged from 2.5 to 17 years (median age 11 years) with high-risk NHL underwent high-dose chemotherapy followed by autoHCT. Initial diagnosis included: NHL B stage III (7), NHL B stage IV (14), NHL T stage III (4), NHL T stage IV (2), LCAL (11). Twenty-eight patients were transplanted in complete remission (15 in 1st CR, 11 in 2nd CR and 2 in 3rd CR). Ten patients were transplanted in partial remission (5 in 1st PR, 3 in 2nd PR and 1 in 3rd PR).

Conditioning regimens were as follows: BEAM (n=33), BCNU+VP16+CY (n=3), BU+VP16+CY (n=2). Thirty-six children were transplanted with peripheral blood progenitors, one received bone marrow and one bone marrow and peripheral blood stem cells. Results: Thirty one patients (81.5%) are alive with follow up ranging from 2.5 months to 6.5 years (median 22 months), 25 (65.8%) in CCR. Seven children died four due to disease progression, one after subsequent MUD BMT and two due to infectious complications (TRM 5%).

EFS for the whole group reached 0.64 and no event was noted after day + 344. EFS according to initial diagnosis was 0.8 for NHL B, 0.45 for LCAL and 0.44 for NHL T. Children transplanted in CR had better prognosis in comparison to those in PR (EFS 0.69 vs 0.5, difference n.s.).

We conclude that high-dose chemotherapy with autoHCT is feasible, safe and results in prolong remission in high proportion of patients, even those transplanted without CR.
5. Hodgkin’s Disease

CLINICAL PRESENTATION, SURVIVAL AND PROGNOSTIC FACTORS IN ADULT HODGKIN’S DISEASE – RESULTS FROM A DEVELOPING COUNTRY

T.G. Sagara, P.S. Sreedharana, S.G. Ramana
Cancer Institute, Chennai, India.

A total of 320 adult patients were treated between the years 1980 and 1995 at the Cancer Institute, Chennai, India. There were 243 males and 77 females patients. The age group ranged from 15-76 years. Majority of the patients (65%) presented with cervical lymph node presentation. B symptoms were present at diagnosis in 57.2% of patients. Majority of these patients were of mixed cellularity histology (48.6%). The next commonest histology was lymphocyte depletion (24.6%). Staging laparotomy was practiced in the earlier part of the analysis and it upstaged the disease in 12 patients. Most of the patients were in clinical stage II or III (29% and 42% respectively). CR was achieved in 74% of the evaluable patients. The OS at 5 years and 10 years were 72% and 65% respectively. Multivariate analysis done for prognostic factors revealed that female sex, attainment of CR and nodular sclerosis histology were good prognostic factors, while age above 40 years and stage IV disease were associated with poor outcome. Factors like relapse did not significantly change overall survival.

HIGH QUALITY OF CHEMOTHERAPY (CT) IN UNSELECTED PATIENTS WITH HODGKIN’S DISEASE (HD), A REGISTRY BASED STUDY IN THE NORTHERN NETHERLANDS

M.K. Bakker, M. Schaapveld, M.B. Beijer and G.W. van Imhoff
Comprehensive Cancer Centre North Netherlands and Departments of Radiotherapy and Hematology, Groningen University Hospital, Groningen, The Netherlands.

Introduction: To improve and standardise treatment outside the controlled setting of a clinical trial of patients with HD in hospitals in the North Netherlands a guideline for staging and treatment, including a dose and administration schedule for CT was developed. In this study the adherence to the guideline was assessed by evaluating the quality of CT administered in unselected patients treated for HD. Methods: From our population based registry, containing all cancer patients in the North Netherlands, 316 patients with HD, aged 215 years, diagnosed between 1980-1995 were identified. Data on diagnostic procedures, staging and precise data on the administered treatment were collected from the patient records. 121 pts (38%) were treated with MOPP/ABV hybrid outside the setting of a clinical trial in accordance with the prevailing guideline. Patient characteristics: male 58%; median age 36 years (range 16-80); stage I/II favourable 4%, III/IV unfavourable 58%, HIV 55%. Quality of administered CT was studied by computing dose-delay and -reduction, and the relative administered dose intensity (RDI) for each individual drug according to Hryniuk. Results: 109 patients were evaluable, 12 patients were excluded due to insufficient data. 103/109 patients (94%) completed the CT (6-8 courses). Discontinuation (< 6 courses) was caused by toxicity in 4 patients; 2 patients died before the end of the treatment. 63/103 patients (61%) experienced at least once either a dose-reduction of at least 25%, and/or a delay of at least 1 week during treatment. The median overall RDI was 88% (inter quartile range IQR =82-93). The mRDI for mechloretamine, doxorubicin, procarbazine and vinblastine (91%, IQR =85-96) was significantly higher than for vincristine (69%, IQR =60-77) (p<0.01). Sex (male: mRDI=87%; female: mRDI=90%), age (<40: mRDI=88%, 40-60: mRDI=87%), stage (I/II: mRDI=89%; III/IV: mRDI=88%), or year of treatment (1980-1990: mRDI=87%; 1990-1995: mRDI=88%) did not correlate with the quality of administered CT. Conclusion: Although 61% of patients who completed MOPP/ABV CT had at least one delay or dose-reduction during CT, the mRDI of the drugs most active in HD was 91%. By using transparent guidelines it is possible to achieve a high quality of administered CT, outside the controlled setting of a clinical trial in patients with HD.

THE VALUE OF A CENTRAL MULTIDISCIPLINARY RADIOLOGICAL REVIEW IN THE HD12 TRIAL OF THE GERMAN HODGKIN LYMPHOMA STUDY GROUP (GHSG)

H.T. Enss, S. Staar, A. Grossmann, A. Engert, J. Franklin, B. Krug, V. Diehl, R.-P. Müller
Department of Radiation Oncology, 3Radiology, 4Medical Oncology, University of Cologne, Germany.

Introduction: The HD12 protocol is a multicentric prospective randomised trial of the GHSG for advanced stages of Hodgkin’s disease. Beside a randomization for different intensities of chemotherapy (CTX) using the BEACOPP-scheme, the indication and efficacy of additive radiotherapy (RT) to initial bulky and/or areas with residual disease is tested in a randomized setting.

Methods: All study participants are asked to send all diagnostic imaging as well as written protocol forms of their HD12-patients to the reference center. Here, a multidisciplinary panel of radiotherapists, radiologists and medical oncologists reviews, blinded to treatment arms, the diagnostic imaging with comparison to the documentation forms. For patients with poor response to CTX, the panel may recommend RT independent of the randomization. Additionally, the panel evaluates the quality of CT in this multicenter study. Since 7/1999, a total of 2607 CT of 371 pts. (head&neck 28%, chest 39%, abdomen 33%) have been evaluated.

Results: 42% of all CT were performed in non-university hospitals, 28% in university hospitals, and 30% in private institutions. According to imaging quality the contrast enhancement was good in 77%, moderate in 15%, and poor in 8%. CT-imaging from university hospitals was valued superior than that from other institutions (p<0.001). Compared to the written disease documentation, the panel assessed different extensions of disease in 814/2607 CT. These diagnostic findings would result in a change of stage in 175371 pts. (5%). After CTX 16371 pts. (45%) showed residual disease (≥1.5 cm), and for 53371 pts. (14%) the panel recommended additional RT independently from the randomization arm.

Conclusions: Patients with Hodgkin’s disease receive high quality of imaging, especially CT. A central independent multidisciplinary panel may markedly improve quality assurance for these study patients.

EPIDURAL INVOLVEMENT IN HODGKIN’S DISEASE

Zsófia Milényi, Árpád Illés, Lajos Gergely, László Milényi
3rd Dept of Internal Medicine, 3Radiology Department, Medical and Health Science Center, University of Debrecen, Hungary.

Introduction: Epidural involvement is a rare manifestation of Hodgkin’s disease (HD). This manifestation occurs in approximately 0.6-7.2 % of patients with HD.

Methods: We examined epidural involvement retrospectively among 512 primary treated and followed up patients with HD from 1970 to 1999.

Results: In one case (0.2%) epidural manifestation was the first symptom and in six cases (1.2%) it occurred later, disseminated stage. Every patient was male, three mixed cellular and four nodular sclerosis histological type. The thoracic segment in four cases, the lumbar in two and the cervical segment in one case was involved. In the diagnosis and planning the treatment computer tomography, MRI and myelography were used. Significant functional improvement with complete remission from 6 to 100 months was achieved by laminectomy, loco-regional irradiation and polychemotherapy. Experiences with this rare manifestation of HD were compared to data in the international literature.

Conclusions: It must be emphasised interdisciplinary approach in these patients’ treatment, with co-operation among oncohaematologist, neurologist, radiologist, neurosurgeon, radiotherapist and physiotherapist.
Uncommon sites in initial involvement of Hodgkin’s Disease.

G. Pito, P. Cauola
Hematology Division. A. Busico Hospital, Cagliari, Italy

Introduction: At a primary diagnosis, extranodal involvement is present in approximately 10-15% of HD cases. Skeletal involvement is present in about 1% of the above patients, while primitive cutaneous involvement is sporadic, as is the case in less frequent sites like the thyroid, the parotid or when limited to the spleen.

In the following report we will discuss 12 cases of primary extranodal HD.

Statistics: from 1984 to 2001 we’ve diagnosed close to 340 cases of HD among which we found 12 cases of atypical extranodal involvement: 7 were located exclusively in the bone, 2 in the thyroid, one was cutaneous, one was located in the parotid and one was limited to the spleen.

In 5 cases the organs involved were the sacral vertebrae and the pelvis, one involved the scapula and another one the extraordinary primitive location in the pubic bone.

The histologic subtype in 8 cases was NS, in two cases it was CM while the remaining two couldn’t be further classified.

The case involving the spleen was particular: diagnosed with AIHA, non-responsive to immune suppressive therapy with Prednisone and Cyclophosphamide, the underwent splenectomy which provided an HD diagnosis. When treated with chemotherapy, COPP regimen, RCC was attained.

Therapy: Treatment in 8 cases was ABVD, in 2 cases MA-MA, Stanford V in one case and COPP in another one. In 6 of the 12 cases therapy was consolidated with radiotherapy.

Conclusion: The presence of extranodal HD in our statistics is considerably higher than others’, while treatment was the conventional one employed and obtained similar results.

SCD30 PREDICTS POOR OUTCOME IN HODGKIN’S DISEASE:

Authors: T-Mainou Fowler, P Taylor, S Miller, F Jack, S J Proctor,
Address: University of Newcastle, Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne.

Introduction - With improvements in treatment in HD the number of patients who fail treatment is small but it is important to recognise these patients at diagnosis so that more intensive treatment can be given.

Methods - Patients with histologically confirmed classical HD had serum taken at diagnosis and levels of LDH, b2M and sCD30 (assayed using paired antibody enzyme linked immunoassays (ELISA)). The levels were then correlated with patient outcome (event free survival).

Results - 141 patients (57 females/84 males) age 8 – 80 median 37 years were included in the study, with median follow up 18 months, range 3 - 72. LDH was not found to be predictive of survival and did not correlate with either b2M or sCD30. b2M and sCD30 levels showed weak correlation but sCD30 (levels < or > 50) did predict for event free survival, (median event free survival undefined vs 41 months) p<.009. This was independent of age.

Conclusion - Low sCD30 is a stronger predictor for event free survival than LDH or b2M and it’s addition to clinical prognostic indices should be explored.

PROGNOSTIC FACTORS IN ADVANCED HODGKIN’S DISEASE

M. Badea, Daniela Badea; University of Medicine and Pharmacy, Craiova 1100, Romania

Introduction: Haseklevier identified seven prognostic factors in the advanced Hodgkin's disease as statistically significant in a Cox regression model. The aim of the study is the assessment of the prognostic prediction degree of these prognostic factors on our patients with advanced HD.

Methods: 61 adult patients with HD CS IIIA (26.50%), IIIB (28.25%), IVa (9.81%) and IVB (17.46%) including 11.11% patients with IIIB or II bulky disease was treated in our unit. The gender ratio was 1.17 for males. Mean age: 38 years. As regard the histologic type 1.38% had lymphocyte predominance, 31.74% nodular sclerosis, 46.03% mixed cellularity, 4.76% lymphocyte depletion and 13.87% unclassified Hodgkin's disease. The protocol included 3 courses of CHUVPP (ivince: 1994) or ABVD associated with local radiotherapy (24-32 Gy) on the massively affected or difficulty responding regions plus 3-5 cycles of chemotherapy. In cases with bulky mediastinal involvement, the radiotherapy regimen involves 40 Gy.

Results: 17.66% of patients presented leukocytosis of more than 16000/mm³, 14.28% lymphocytopenia of less than 600/mm³ or less than 8% of the leukocyte counts, 47.94% albumin levels less than 4 gr/l and 22.22% hemoglobin levels less than 10.3 gr/l. 19.49% of patients were older than 65 years, 63.49% were males and 71.47% had B symptoms. The complete remission rate was 92.06%; the relapse-free survival and overall survival were 77.58% and 84.48% at 5 years. Univariate analysis does not validate any of these parameters as carrying a prognostic significance, but the addition of three or more factors of negative prognostic associates with a high 5-year relapse rate (36.36% x 11.11% - Fisher exact p<0.06) and death rate (27.27% x 8.33% - Fisher exact p<0.06).

Conclusion: A prognostic assessment system of cases with advanced HD is necessary in modulating the intensity of the therapy protocol. Cases with unfavorable prognostic would have an aggressive therapeutic approach, helping to prolong the duration of survival, while cases with favorable prognostic would be submitted to a less intense therapy, in order to limit the long-term toxic effects.

INTERLEUKIN-18 SERUM LEVELS IN HODGKIN DISEASE

Dept. of Biomedical Sciences, Section of Hematology, University of Catania, Italy

Interleukin-18 (IL-18) is a novel cytokine synthesized by activated macrophages. High levels of this cytokine have been found in patients affected by non-Hodgkin lymphomatoid and acute lymphoblastic leukemias (Takubo, Acta Haematol 2000). Injection of IL-18 in mice induces significant neutrophilia, lymphopenia and eosinophilia (Ogura, Blood 2001), a condition reminiscent of the hematological picture of Hodgkin disease. Therefore, we evaluated the IL-18 serum concentration in 18 Hodgkin patients at diagnosis. Eight of them (44 %) showed a IL-18 serum level higher than the upper normal limit. No significant correlation has been found between IL-18 levels and stage of disease or any of the laboratory and clinical features tested, including disease, absolute number of neutrophils, eosinophils, lymphocytes, Hb, PLT, albumin, bulk mediastinum, histology, and B-symptoms. All patients have been treated with ABVD for at least 4 cycles ≥ RT. However, only 4 of the 8 patients with high IL-18 obtained a complete response vs 9 out of 10 patients with normal IL-18 serum concentration (Chi Square P-value 0.05). These preliminary results may indicate that IL-18 could be involved in the complex cytokine network of Hodgkin disease and its serum level might have prognostic significance.
Interleukin 13 (IL-13) is detected at a Low Frequency in Serum From Patients With Hodgkin Disease (HD). P. W. M. Elstrom, C. B. Caballitas, and A. Younes. Department of Lymphoma/Myceloma, M.D. Anderson Cancer Center, Houston, TX, 77030.

Introduction: Interleukin 13 (IL-13) has recently been found to be highly expressed in cultured Hodgkin disease (HD)-derived cell lines and primary Hodgkin and Reed-Sternberg (H/RS) cells. Furthermore, IL-13 has been detected in the supernatants of HD-derived cell lines by enzyme-linked immunosorbent assay (ELISA), and neutralizing antibody to IL-13 results in inhibition of H/RS cell proliferation in vitro. Because of the potential therapeutic implication of these observations, we examined IL-13 levels in serum from patients with newly diagnosed and relapsed HD and healthy volunteers.

Methods: Supernatants from 3 HD-derived cell lines (HD-LM2, L-428, and KMH-2) known to produce IL-13 were used as positive controls. The sensitivity of the ELISA assay was less than 12 pg/mL.

Results: All 3 HD cell lines produced IL-13 (range 85-300 pg/mL). In contrast, IL-13 was below the detectable level in sera from 40 healthy individuals tested. Subsequently, we examined IL-13 levels in sera from 108 newly diagnosed patients with HD (70% had nodular sclerosis histology). Thirty-one (28%) had B symptoms, and 36% had stage I/II disease. IL-13 levels were elevated in sera from 11 (10%) of 108 patients (range 34 to 82 pg/mL). However, IL-13 levels did not correlate with B symptoms, disease bulk, histologic subtype, advanced Ann Arbor stage, or shorter disease-free survival. Of the 11 newly diagnosed patients who had elevated serum IL-13 levels, only one patient experienced disease progression, 4 months after completing therapy for stage III/IV bulky disease. We also studied IL-13 levels in sera from 31 patients with relapsed HD. Five (16%) had elevated IL-13 serum levels (range 42 to 48 pg/mL).

Conclusions: Our data show for the first time that IL-13 levels can be elevated in the serum of patients with HD. Although the number of patients with elevated IL-13 levels is small, this does not rule out the possibility of higher concentrations at disease sites. Our data may serve as the basis for new treatment strategies to explore the potential clinical relevance of IL-13 in patients with HD.

Hodgkin's Disease: Incidence of Rogue Cells in Peripheral Blood: Lympocytes and Relationship with clinical outcome

M'Cacher R¹, Girinsky T², Carde P², Rubrig V², Dossou J¹, Violot D, Beron-Guillard N, Koeckste S, Parmeuter C³

1Department of Medicine 2Department of Radiation Oncology 3Laboratory of Radiosensitivity and Radiocarcinogenesis: UPRES EA 2710 4Department of bio-statistic INSTITUT GUSTAVE ROUSSY, 94805 Villejuif France

Purpose: To assess a correlation between the clinical outcome and the frequency of rogue cells in peripheral blood lymphocytes of Hodgkin's disease patients. Patients and Method: 49 Hodgkin's disease (HD) patients were included in this study. Twenty healthy donors and 69 untreated cancer patients served as controls. Rogue cells were scored in peripheral blood lymphocytes sampled before and after chemotherapy (CT), after radiotherapy (RT) and at several time intervals till 2 years after treatment using chromosome 1, 3 and 4 painting (FISH). Results: Before treatment, the frequency of rogue cells in HD patients (1 rogue cell in 3542 scored cells) was similar to that observed in controls (1 rogue cell in 5670 scored cells). Twenty two patients exhibited rogue cells after CT and RT. The frequency of rogue cells increased significantly after CT (P<0.001) and after RT (P=0.02), but was not significantly related to the disease stage, the CT regimen, treatment doses administered (RT and CT) or size of irradiation field. After a median follow-up period of 24 months (range 18 to 48 months), 10 of 22 patients exhibiting rogue cells relapsed versus only one of 28 patients not exhibiting rogue cells (P=0.0001). Six of 22 patients exhibiting rogue cells versus one of 28 patients not exhibiting rogue cells developed late complications (P=0.001). Conclusion: The presence of rogue cells is presumably associated with viral infection (CT virus) interfering with p33. This presence is significantly correlated with higher risk of relapse and possibly, with the occurrence of late complications in HD patients and may play a contributory role in the origin of secondary malignancies characterized by clonal chromosomal aberrations in other tissues or in lymph nodes. Keywords: Hodgkin's disease, rogue cells, chromosomal aberrations, clinical outcome, relapse, prognostic factor.

GENE EXPRESSION PROFILING DEFINES MOLECULAR SUBTYPES OF CLASSICAL HODGKIN'S DISEASE

E. Devillard, F. Bernucci, R. Bhouabdallah, P. Broursset, R. Houlgate, L. Kerri

Institut Paoli-Calmettes, Marseille, and CHU Purpan, Toulouse, France

Introduction: Although the prognosis of Hodgkin's disease is relatively good, around 20% of patients do not benefit from current therapies and succumb to their disease. A large-scale molecular characterization of disease might help improve HD management.

Methods: Using cDNA arrays, we have studied the mRNA expression levels of ~1000 selected genes in 34 benign and malignant lymphoid samples including 21 classical Hodgkin's disease (HD) tissue samples.

Results: Hierarchical clustering identified 3 main molecular groups of HD tumors relevant with respect to histology, response to therapy and clinical outcome. Samples from all bad outcome HD (BOHD) patients clustered in one group whereas the two other groups contained most good outcome HD (GOHD) cases. The GOHD nodular sclerosis samples overexpressed genes involved in apoptotic induction and cell signalling, including cytokines, while the BOHD samples were characterized by the upregulation of genes involved in fibroblast activation, angiogenesis, extracellular matrix remodelling, cell proliferation, and the downregulation of tumour suppressor genes.

Conclusions: Our results establish a molecular taxonomy of HD correlating with response to therapy and clinical outcome, thereby suggesting the possibility of improving the current prognostic classification. The identification of discriminant genes represents a basis for new potential therapeutic targets.

MMP-2 AND MMP-9 EXPRESSION, THEIR CLINOCOPATHOLOGICAL CORRELATION AND PROGNOSTIC VALUE IN HODGKIN'S DISEASE

O. Kuitinen, Y. Soini, T. Tarpeenemi-Hujanen

Oulu University Hospital, Dep. of Radiotherapy and Oncology and Dep. Of Pathology, Oulu, Finland

MMP-2 and MMP-9 are matrix degrading enzymes involved in invasion, tissue remodelling, angiogenesis and control of inflammatory response and linked to adverse prognosis in several solid tumors. However in AML MMP2 expression is a favorable prognostic factor.

Materials and methods: Paraaffin embedded histological sections from 67 adult patients with newly diagnosed Hodgkin's disease were stained immunohistochemically with MMP-2, MMP-9 and factor VIII antibodies (detecting tumor vasculature). Correlations of the results with clinical disease presentation were studied.

Results: MMP expression did not correlate with disease stage, occurrence of extranodal infiltrates, or occurrence of bulky tumor. MMP-9 expression correlated, however with B-symptoms and had an inverse correlation with the extent of neovascularisation. MMP-2 expression correlated with favorable prognosis (P=0.0167) and MMP-9 expression showed a tendency towards an unfavorable prognosis. Combining results of both of the stainings enhanced their prognostic value and separated patient categories with between 58% and 100% chance for 7 y survival (P=0.0247).

Conclusion: Our results suggest that MMP index could be a clinically relevant prognostic factor in Hodgkin's disease and should be studied in larger patient population.
NODULAR PARAGANULOMA TYPE OF T-CELL RICH B CELL LYMPHOMA: A DISTINCT CLINICOPATHOLOGICAL PHASE DURING THE TUMOUR PROGRESSION OF NODULAR LYMPHOCYTIC PREDOMINANT TYPE OF HODGKIN DISEASE? K.N. Narang and P. Ranjan. Lymphoma Registry, Department of Pathology, Tata Memorial Hospital, Mumbai, India

Introduction: Hodgkin disease - nodular lymphocytic predominant type (HDNL) has morphological overlap with T cell rich B cell Lymphoma (TCRBL). Progression of HDNL, in a proportion of cases to TCRBL is known. The present study stemmed from our observation that some of the 'grey zone' cases depicted nodular lymphoid proliferations with an abundance of L&H cells and had a marked paucity of small B-cells within the nodules. Most such cases had high stage disease at presentation.

Methods: We identified 19 similar cases and studied their clinical features.

Results: They were 14 - 73 years of age (mean: 42 years) and 18/19 were men. Extranasal presentation and mediastinal lymphadenopathy were absent. Hepatic/spenic involvement was noted in five cases. Pleural effusion and ascites were noted in one case each. Bone marrow involvement was seen in 5 of 11 patients. 10 of 14 patients had Ann Arbor stages III or IV. None presented in Stage I. 57% of cases had B symptoms.

Conclusion: This pathologically identifiable entity with resemblance to HDNL is more aggressive disease.


Background: In unfavorable stage IA and IIA Hodgkin's lymphoma (HL), the good results obtained with ABVD plus involved field radiotherapy are counterbalanced by the late cardiac and lung toxicity. AIM OF THE STUDY: To test in this set of patients the results of the low aggressive and low toxic EVE regimen, in comparison to ABVD. PATIENTS AND METHODS: From January 1996 to March 2000, 189 stage IA or IIA HL patients were randomized to receive 4 courses of either ABVD or EVE. They presented one or more of the following prognostic factors: bulky disease, lymph-node areas >3, ESR>40, B lesion, hilar involvement, infradiaphragmatic involvement. In both arms chemotherapy was followed by involved field radiotherapy (36 Gy). ABVD was administered according to the original schedule (Bonadonna et al Ann Intern Med 1983). EVE was scheduled as follows: epidurabine iv. 70 mg/m^2 on day 1, vinblastine iv. 6 mg/m^2 on day 1, etoposide iv. 100 mg/m^2 on day 1 followed by etoposide on 120 mg/m^2 from day 2 to 3. The cycles were repeated every 21 days. 174 patients (85 in the ABVD and 89 in the EVE arm) are so far evaluable for toxicity and response and are the object of the present report. RESULTS: Prognostic variables (sex, age, stage, bulky disease, histology, Hb, ESR, LDM) are comparable between the two groups. Both regimes were well tolerated and there were no differences of acute hematological and extra hematological toxicity. Remission rate (RC) at the end of the chemotherapy was similar in the two arms (ABVD 69% vs. EVE 66%, p=0.3). Moreover no different CR rates were seen at the end of the whole program (ABVD 93% vs. EVE 88%, p=0.1). The 5-year actuarial relapse free survival rate was higher in ABVD than in EVE arm (ABVD 93% vs. EVE 76%, p=0.01). Moreover the 5-year failure free survival rates were as follows: ABVD 87%, EVE 66% (p=0.01). So far overall survival rates were not different: ABVD 98%, EVE 87% (p=ns). CONCLUSIONS: The EVE regimen showed a high relapse rate. In unfavorable stage IA and IIA HD a treatment strategy less intensive than 3 or 4 ABVD plus involved field radiotherapy can be associated with a high relapse rate.

ABVD CHEMOTHERAPY WITHOUT OBLIGATORY RADIOTHERAPY IN PATIENTS WITH EARLY AND INTERMEDIATE STAGE HODGKIN'S LYMPHOMA. R. Naumoff1, A. Haertel1, F. Kroschinsky1, B. Behlmann-Baumann1, S. Freund1, M. Diewe1, T. Hermann1, F. Flieder1, G. Schrader1 and M. Haenel1.1Department of Internal Medicine I, 2Department of Nuclear Medicine/PET Centre Rossendorf, 3Department of Radiotherapy, University Hospital Dresden, 4Division of Hematology, Klinikum Chemnitz, Germany.

Introduction: Combined treatment modality using ABVD chemotherapy and involved field radiation is effective in patients with early and intermediate stage Hodgkin's lymphoma. The aim of our prospective study was to reduce the toxicity by omitting the subsequent radiotherapy in patients with complete remission (CR) after ABVD. Methods: Since May 2000 a total of 23 patients (median age 33 years, range 17-71; 18 male, 5 female) with early (n=12) or intermediate stage (n=12) Hodgkin's lymphoma (HL) were treated either with 4 or 6 cycles of ABVD. A consolidating involved field radiation (30 Gy) was performed only in patients who achieved less than CR following chemotherapy. Results: After finishing ABVD 17 patients (74%) showed a CR. Twelve patients with CR were investigated by PET scan, in 1/12 cases PET showed a negative result. The remaining 6 patients with partial response after chemotherapy went into CR after radiotherapy. The observed side effects were comparable to the well known moderate toxicity of ABVD. After a median follow-up of 13 months all patients are alive in continuous CR. Conclusions: 4 or 6 cycles of ABVD chemotherapy induce high CR rates in patients with early and intermediate HL. This strategy could reduce combined toxicity in a high proportion of patients. However, the results are preliminary and should be confirmed in a larger number of patients and with a longer follow-up.
BULKY MEDIASTINAL HODGKIN'S DISEASE: A DECADE EXPERIENCE WITH A COMBINED MODALITY APPROACH.

Introduction: Bulky mediastinal involvement is a challenging presentation of Hodgkin's disease (HD) with a negative prognostic significance when the disease is treated either with radiotherapy (RT) or chemotherapy (CT) alone. Therefore, combined modality therapy (CMT) following clinical staging has emerged as the treatment of choice. In this multicenter retrospective study we present the Greek experience of the last decade regarding the treatment of this subgroup of HD with CMT. Methods: Between 1990 and 2000, 101 newly diagnosed patients (79 males, 72 females), aged 14-75 years (median 24), with bulky mediastinal HD have been treated with CMT. The predominant histology was that of nodular sclerosis (88%). The clinical stage was I in 5%, II in 80%, III in 12% and IV in 2% of pts. B symptoms had 79% of pts and extranodal involvement 7%. All pts were treated with CT (ABVD:69%, MOPP/ABV hybrid:20%, alternating MOPP/ABVD: 12%) and RT (Extended field: 40%, Limited field: 60%). Results: Of the 101 patients 96 (95%) achieved a complete remission (CR), and 4 a partial remission, while one had refractory disease. The CR rate was 83%, 100% and 92% for patients treated with ABVD, hybrid MOPP/ABV, and alternating MOPP/ABVD. Seven out of 96 (7%) complete responders relapsed. Overall, 6 patients have died of progressive disease, 4 are alive with active disease and 91 are in continuous CR. Two patients developed secondary malignancies both in the ABVD group (acute myelogenous leukemia and non-Hodgkin’s lymphoma). With a median follow up time of 72 months (I-148), the OS and EFS were 86% and 93% respectively with no difference among the three CT groups. Conclusions: HD with bulky mediastinal involvement is mainly of NS histology and affects mostly young females. An anthracycline-based CMT is an efficacious therapy of this form of HD. Given its equivalency to 7-8 drug regimens, ABVD plus limited field RT should probably be the treatment of choice for this challenging group of patients. Secondary tumors were rare but further follow-up is warranted.

LOPP/EVA: AN EFFECTIVE CHEMOTHERAPY REGIME IN PATIENTS WITH UNFAVORABLE LOCALIZED HODGKIN’S LYMPHOMA: PILOT TRIAL.

Introduction: The efficacy and toxicity of LOPP/EVA chemotherapy in the treatment of patients with HD was evaluated. Methods: Between 05/1997-12/2000 40 patients with Hodgkin's Lymphoma were recruited. Median age of the patients was 27 (range 15-51), 7140 (42.5%) patients were male, 28(60%) patients had B symptoms. Stage of entry to the study included stage I 3/40 (7.5%), stage II 21/40 (52.5%), III-B 7/40 (17.5%), IV-A 2/40 (22.5%). Mediastinal masses were present in 21 (52.5%) pts, 77.5% had nodular sclerosis. LOPP/EVA regimen consists as follows: Vincristine 1 mg/m2 iv d 1, Etoposide 75 mg/m2 p.o d 1-5, Chlorambucil 6 mg/m2 p.o d 1-7, Prednisolone 90 mg/m2 p.o d 1-7, Mopemykline 50 mg p.o d 1-7. Adriastrines 50 mg/m2 iv d 1, 8, every 28 days for 6-8 cycles. Results: A median of 6.5 cycles of LOPP/EVA were given per patient, for a total of 255 cycles. 75% patients received radiation to sites of bulky disease, after chemotherapy: total dose: 33-39 Gv. Toxicity was acceptable: grade III neutropenia occurred in 20% of cycles, IV in 15% of cycles; grade III infections in 27% of cycles. Antibiotic therapy was given with 66 cycles (36%) of LOPP/EVA for infection, G-CSF (Neupogen) was given post 74 (36%) cycles. Grade III-IV anemia occurred in 4.5% of cycles. 8 patients (20%) required red blood cell transfusions, one patient-three times. Other toxic effects: neuropathy grade IV in 3 cases (7.5%). No toxic death was observed. The median duration of treatment was 7.6 months (range 4 to 12 mos), and median follow-up: of 44 months (range 26-54 months), 31/40 (77.5%) patients achieved CR, 9 patients progressed after treatment. 5 patients died of HD. At the time of this analysis 35 out of 40 patients were alive, 31 in CR. OS and DFS will be presented. Conclusions: LOPP/EVA was found to be active, tolerable chemotherapy regimen for unfavorable localized Hodgkin's Lymphoma.

A STAGE-MODULATED LOW TOXIC REGIMEN (VEBEP) PLUS LOW-DOSE RADIOTHERAPY (RT) FOR HODGKIN'S DISEASE (HD).
Department of Medical Oncology & Hematology, Clinica Humanitaria, Rizzonano (Milan) and *Division of Medical Oncology A. Aviano-ITALY.

Following the encouraging results of our previous VEBEP and of single agent vinorelbine (VNR) in pretreated HD, a new VEBEP regimen was developed at our institutions with the primary aim to reduce short and long-term toxicity and, if possible, to improve therapeutic outcome. The regimen consisted in epirubicin 30 mg/m2 iv day 1-3, cyclophosphamide 1000 mg/m2 iv on day 1, VNR 23 mg/m2 iv on day 2, biotinylcyclin 10 mg/m2 iv on day 3, and prednisone 100 mg iv day 1-3. Courses were given outpatient every 21 days without growth factor support. Treatment plan varied according to Ann Arbor/105 stage: early stage (I-IIA + E) were given two courses followed by involved-fields (IF) RT 25-30 Gy, intermediate stages (IIIB-I-IA-BX + E, IIIA1) were given four courses of VEBEP and IF-RT at same doses, and advanced stages (all others) were given six courses of VEBEP with RT only on bulky sites. RT was delivered only if complete remission (CR) was confirmed by restaging procedure at the end of each chemotherapy program. Of 98 to 66 consecutive patients were accrued. Thirty-five were female and 52 male, with a median age of 36 years ranging from 15 and 70. Eleven had limited, 17 intermediate and 39 advanced stage OM 62 patients evaluable for response 56 obtained CR/CR-U. Toxicity was globally mild. No patient was hospitalized for management of toxic effect, and no patient but one received RBC transfusion. A total of 27 courses of 256 delivered were given at reduced dose or delayed due to incomplete hematological recovery. Fever, myositis and peripheral neurotoxicity never exceeded grade II. After a median follow-up of 15 months (range 1-49), ten patients with relapse (N=3) or resistant disease (N=7, defined as non-CR) underwent 2nd line treatment. Thus, partial freedom from progression and overall survival, are 100%, 86%, 89% and 100%, 100% and 78% for the three prognostic groups, respectively. In conclusion, VEBEP chemotherapy is highly effective in HD and carries a low-acute toxicity profile. Longer follow-up is needed to confirm therapeutic results and to evaluate long-term sequelae. An increase in dose-intensity could be planned for patients at higher risk.

TAII00ED BEACOPP REGIMEN FOR STANDARD AND HIGH RISK HODGKIN Lymphoma BASED ON EARLY RESPONSE TO GA+ SCINTIGRAPHY AND THE INTERNATIONAL PROGNOSTIC SCORE FOR ADVANCED DISEASE (IPS).
E. Dang, N. Halm, M.H. Kirschbaum, D. Lichten*, O. Iarel, J.M. Rowel, R. Eppenberger, *Days of Hematology and BMRI, 60 consecutives patients were accrued. Treatment was started on about 2001. A protocol was developed at the Ramsey Med Care for patients with non-favorable HD, using escalated BEACOPP only for those with multiple poor prognostic features at diagnosis or for others if they failed to demonstrate an early response as measured by 18F Sodium Fluoride PET/CT. A second treatment approach was followed with clinical stage III of IV. Each patient was categorized according to the IPS scoring system (Hasenclever et al, NEJM, 1998). Pts with standard risk having 2 factors were allocated to receive 2 cycles of BEACOPP. Patients with >2 risk factors were divided into 3 subgroups: treatment was modified to regular BEACOPP as of the third cycle. If the gallium scan was still positive, pts received 4 additional cycles of escalated BEACOPP for a total of 6 cycles. 33 pts had advanced disease and 17 had early unfavorable disease. 24 pts started treatment with regular BEACOPP. 2/3 had a >10% gallium scan following the 1st cycle and their therapy was thus escalated. Sixteen pts were started with escalated BEACOPP. In this group 9/16 pts had a negative gallium or FDG scan post 1st cycle and treatment was changed to regular BEACOPP. Toxicity: Thirty episodes of grade IV neutropenia were seen. Dose was modified in 15 cycles of escalated BEACOPP. One pt had a sudden death at home after 4 cycles of standard BEACOPP. In summary, tailored BEACOPP may be useful to reduce the cumulative dose of potentially toxic and leukemogenic chemotherapy. It is suggested that response to Ga+ or FDG scintigraphy be used as an additional index to tailor therapy. To date, 4 patients have relapsed (8%) with albeit a short median follow-up of only 19 months. Further follow-up is required to evaluate the DFS, late toxicity and leukemogenicity of this regimen.
HODGKIN’S DISEASE IN THE ELDERLY: A POPULATION BASED STUDY

Authors: G.L. Stark1, K.M. Wood2, F. Jack1, B. Angus2, S.J. Proctor1, P.R. Taylor1.

Departments of Haematology1 and Department of Pathology2, Royal Victoria Infirmary, Newcastle upon Tyne, England.

Introduction: The incidence and outcome in older patients with Hodgkin’s disease (HD) is poorly described. We present the results of a population-based study in the former Northern Health Region of England (pop. 3.08 million) between January 1991 – December 1998.

Methods: All patients with newly diagnosed HD in the region are registered centrally and followed up to death. We review the outcome in all patients aged 60+ years.

Results: 521 patients were diagnosed, 102 (20%) were aged 60+ years. 52 men, 50 f, aged 60 – 91 years. 89 had classical HD, 8 had NLPHD and in 5 subtype was unclassifiable. Median FUs was 63 months (range 20 – 113).

The age-specific incidence was 1.97/100,000 for those aged 60-69 and 2.18/100,000 for those aged 70+ years. Of 95 treated patients, 70 (74%) obtained CRGPR. In the 60-69 year old group disease specific survival (DSS) was 100% for those with early stage disease, and 52% for those with advanced stage in those aged ≥ 70 years, 5 year DSS was 36% and 14% respectively.

Survival of patients with EBV+ tumours was significantly poorer than in those with EBV- tumours (p=0.007); median survival 20 months vs undefined, (patients with EBV+ tumours were more likely to have advanced disease stage (p=0.0008). 47 patients had a HD-related death. 42 died due to relapse/progressive disease and were likely to be treatment-related, all in patients 70+ years.

Conclusion: This study demonstrates that the prognosis in older patients, particularly those with advanced stage disease is poor. Novel approaches to assessment and treatment are necessary in this age group.

RADIATION THERAPY IN EARLY STAGE HODGKIN’S DISEASE, LONG TERM RESULTS AND ADVERSE EFFECTS


VU University Medical Center; Comprehensive Cancer Centre, Amsterdam, The Netherlands.

Introduction: Extended field Megavoltage radiotherapy (RT) produces good survival rates in early stage Hodgkin’s Disease (HD). However, recurrences occur in 30% of the patients and RT induces several late effects like early coronary artery disease, hypothyroidism, but most importantly second malignancies.

Methods: We reviewed all charts of HD patients stage I-II treated in our institute with extended field RT to determine survival, freedom from relapse, salvage rate of relapsing cases and prevalence of second malignancies. Retrospectively, 106 HD patients diagnosed between 1975-1995 who received RT as sole treatment, were evaluated.

Results: After a median follow-up of 12 years, thirty recurrences (28%) were seen; 23 occurred within 5 years of initial treatment. Twelve of the recurrences were located inside the radiation field. The relapse-free survival was 78% at 5 years and 72% at 10 years. Of the 30 relapsing patients, 29 received salvage chemotherapy and persistent complete remission was achieved in 90%.

Sixteen second malignancies occurred, the majority more than 5 years after initial diagnosis. They were located in: lung (2), ovary (2), cervix (1), colon (2), breast (3), stomach (1), skin (2), hypopharynx (1) and NHL (2). Until now, seven patients died due to their second tumour. Other causes of death were: HD (4), cardiac diseases (5) and unknown or other reasons (11). The overall survival for all patients was 90% at 5 years and 76% at 10 years.

Conclusion: Extended field RT alone produces satisfactory results in terms of long-term survival, but induces a considerable risk for second malignancies, which increases with years. The majority of second malignancies are found within the radiation fields. The high mortality rate observed in large cohorts of Hodgkin patients calls for a serious re-evaluation of extended RT.

ELDERLY HODGKIN’S DISEASE: RETROSPECTIVE STUDY ON 149 PATIENTS OBSERVED IN OUR INSTIUTE


Elderly HD pts (> 65 years old) have a poor prognosis explained in part by age related variables as co-morbidity, in part by the low compliance and the high percentage of toxic events. Few are data of literature regarding the best treatment in elderly pts affected by HD and restricted the patient number. We have retrospectively evaluated clinical data of 140 patients over 65 years observed in our Institute between 1969 and 2000 because affected by HD. Of them, 48 pts (34%) were excluded from our analysis: 24 pts because entered in a cooperative study (VBFEBMR), 21 for insufficient data, 2 because pre-treated on other centre and 1 for death before chemotherapy start. Thus, 92 pts (60%) could considered for analysis. Patients characteristics at diagnosis and treatment plan are listed in the table below.

<table>
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<tr>
<th>PT</th>
<th>%</th>
<th>RANGE</th>
<th>MEDIAN</th>
<th>CT</th>
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<tr>
<td>PATIENT NUMBER</td>
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<td>21-23</td>
<td>21-23</td>
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<td>60-80</td>
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<tr>
<td>TREATMENT PLAN</td>
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<td>CT+RT</td>
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<td>18-20</td>
<td>18-20</td>
<td>MOPP/PROF</td>
<td>1-2</td>
</tr>
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</table>

Results: 99 of 92 pts (84%) achieved first CR; 10 of them (13%) relapsed at 3-12 months CT (median 5 months) and underwent second spine line therapy: 8 pts died with disease and 2 are alive in second CR 5 years OT. 12 of 92 pts (13%) had progression of disease: of them, 8 pts died with disease and 4 pts were lost to follow-up with disease at 12, 13, 19 and 32 months respectively. 3 of 92 pts (3%), starting therapy in very bad general conditions, died soon after. We have not observed toxic deaths. 11 pts (12%) died in CCR at a median follow-up of six years (1-8 years) for age related causes. In summary, at a median follow-up of 42 months 34 pts (38%) are alive in CCR, 2 (2%) are alive in second CR, 6 (10%) are alive with disease and 30 pts (32%) died. Conclusions: considering the old median age (70 years), our results may be considered encouraging and indicating that elderly patients may be cured. In fact, 83% of patients achieved CR and 58% of pts are alive in CCR at a median follow-up of 42 months. Elderly as well as younger patients could achieve good results with the same chemotherapy regimens on condition that compliance to treatment and co-morbidity are acceptable.
VEPEMB CHEMOTHERAPY IN ELDERLY HODGKIN’S DISEASE PATIENTS.


AIM OF THE WORK. To evaluate the preliminary results of a chemotherapy regimen (VEPEMB) designed for Hodgkin’s lymphoma (HL) in the elderly.

PATIENTS AND METHODS. Between January 1995 and June 2001, 104 HL patients over 65 years were treated at diagnosis according to the VEPEMB schedule: vinblastine 6 mg/m^2 day 1, cyclophosphamide 500 mg/m^2 day 1, procarbazine 100 mg/m^2 days 1 through 5, prednisone 30 mg/m^2 days 1 through 5, etoposide 60 mg/m^2 on days 15 through 19, mitoxantrone 6 mg/m^2 day 15, bleomycin 10 mg/m^2 day 15. The regimen was scheduled every 28 days. Stage I A and IIA pts (low risk) received 3 courses of VEPEMB followed by involved field irradiation. Stage III-BIV pts (high risk) received 6 courses followed by radiotherapy limited to the areas of bulky disease. Adequate follow up data are so far available for 84 pts (40 low risk and 44 high risk), that are the object of the present report.

RESULTS. Mean age was 72 (range 66-81). The distribution of stage was: I 14 (17%); II 33 (39%); III 21 (29%); IV 16 (19%). B symptoms were present in 32 pts (39%). Comorbidity was present in 20 pts (30%). The tolerance to the first three courses was good. 7 out of the 44 high risk pts (16%) needed a subsequent plan modification and/or interruption (course fourth to sixth) for poor tolerance and/or toxicity. The patients treated with six courses experienced at least one episode of neutropenia, but hospitalisation for fever was seldom required and no toxic death was observed. As expected the outcome was different between low and high risk: CR rate 100% vs. 64% (p=0.01); 5-y relapse free survival (RFS) 100% vs. 64% (p=0.01); 5-y overall survival (OS) 72% vs. 29% (p=0.01); 5-y event free survival (EFS) 58% vs. 21% (p=0.01). The only other factor that influenced RFS was the presence of bulky disease: 50% vs. 90% (p=0.04); CR, OS and EFS curves were affected by comorbidity but not by age itself. In multivariate analysis the only two factors that retained an independent prognostic value for CR and OS were stage and comorbidity. CONCLUSIONS. The cure of elderly HL patients is not impossible, even in advanced stage, and VEPEMB is a well tolerated and effective regimen in this set of patients. Stage and comorbidity are the most important prognostic factors.

MYELOABLATIVE (MA) AUTOLOGOUS STEM CELL TRANSPLANTATION (AUTO SCT) FOLLOWED BY REDUCED INTENSITY (RI) ALLOGENEIC STEM CELL TRANSPLANTATION (ALLO SCT) FOR RELAPSED HODGKIN’S DISEASE (HD).


Introduction: The prognosis for patients with relapsed HD treated with MA and Auto SCT is not as good as originally thought secondary to a high relapse rate (40-60%) and incidence of treatment-related mortality (TRM). Auto SCT may provide a graft versus leukemia (GVLV) effect but it is associated with a high incidence of morbidity and mortality (Jones et al, Blood 77:649, 1991). Recently Carella et al (ICO 18:5918, 2000) demonstrated the feasibility of MA SCT in combination with high-dose TBI (15-30 mGy) with low mortality. We evaluated the effect of RI autologous SCT followed by allograft SCT for relapsed HD. MA consisted of Cyvasto (cyclophosphamide 1500 mg/m^2 day 1 x 4 days, BCNU 100 mg/m^2 day x 3 days, Vp-16 800 mg/m^2 day x 3 days) followed by Auto SCT. After recovery, patients with CD34+ HD (3% or 3/3) received 4 weekly infusions of rituximab (375 mg/m^2 dose), and all patients (3/3) received involved field irradiation (2000-3000 cGy). RI allo SCT consisted of fludarabine 30 mg/m^2/day x 5 days, busulphan 1.2 mg/kg/day x 3 days, and Thymoglobulin 2.0 mg/kg/day x 4 days (for UCBT recipients only) followed by Allo SCT (1 related 6/6, 2 6/6). GVHD prophylaxis, FK506 (0.03 mg/kg/CVI) on day 1-60 (wean started) and MMF (1.5 mg/kg/day) day 1+ of 28.

Results: There were 3 HD (2 CR +1 PR after AICE reinduction), 17 age, 18, and 22 years, 1 stage IIA, 1 stage IIB, 1 stage IVB, and the regimen was well tolerated. Following RI allo SCT, myeloablative recovery occurred on day +15 (MRD) day +18, +23 (UCBT), patelet recovery on day +11 (MRD), day +13, too early (UCBT). The first two patients received 100% donor chimerism and NED at day +225, and the third patient is 95% donor chimerism at day +29. One patient developed grade II acute GVHD of the gut. One patient developed limited chronic liver GVHD responding to alternating CSA/steroids therapy.

Conclusions: This pilot study suggests that MA and Auto SCT followed by involved field radiation therapy, monoclonal antibody therapy, and RI allo SCT is feasible, well tolerated in patients with relapsed HD. Larger numbers and longer follow up will be required to determine if this approach will reduce relapse and/or mortality and improve DFS.

IGEV AS PRE-TRANSPLANT INDUCTION AND MOBILIZING REGIMEN IN PRETREATED HODGKIN’S DISEASE (HD).

M Balasorti, M Magagnoli, L Siracusano, B Sarina, L Castagna, I Timofeeva, S Compasso, A Nozza, A Bertuzzi, and A Santoro. Department of Medical Oncology & Hematology, Istituto Clinico Humanitas, Rozzano-Milan-ITALY.

Purpose: In order to induce cytoreduction and to mobilize peripheral blood stem cells (PBSC) in patients (pts) with refractory/refractory HD, we prompted the IGEV regimen.

Methods: IGEV consists in ifosfamide 2000 mg/m^2 IV d 1-4; gemcitabin 800 mg/m^2 IV d 1 & 4; vinorelbine 30 mg/m^2 IV d 1; prednisolone 100 mg/m^2 IV d 1-4, and G-CSF 200 µg s 7-13 or up to PBSC harvest. Treatment program consisted in 4 IGEV cycles (cy) at 3-week interval as induction, followed in responding pts by high dose chemotherapy (HD-CT) with thiopeta (600 mg/m^2 d -3) and melphalan (140 mg/m^2 d -1) with PBSC reinfusion on day 0.

Results: Twenty-nine pts were accrued from 11/97 to 01/01. Main pts characteristics: M/F: 19/10; median age: 30 years (18-59); refractory/refractory HD; median prior regimens: 1 (1-2); prior radiotherapy (RT) 17. Two pts previously treated by high-dose CT and autologous PBSC-transplantation (PBSC-Tx), received non-myeloablative allogeneic PBSCT from identical siblings. After 4 cy of IGEV, 13 pts achieved complete remission (CR) and 12 partial remission (PR) for an overall response rate of 86%. HD-CT converted PR in CR in seven further pts. Median number of CD34+ cells collected was 6.6 x 10^9/kg (range 0.9-23) after a median of two (range 1-3) apheresis procedures.

Conclusions: IGEV is a very effective cytoreductive and mobilizing regimen with acceptable toxicity in pts with refractory/refractory HD eligible to PBSC-Tx.
SINGLE OR TANDERN AUTOLGEO STEM CELL TRANSPLANTATION (ASCT) ACCORDING TO PROGNOSTIC FACTORS AT FIRST HODGKIN LYMHOIMA (HL) PROGRESSION: A PROSPECTIVE STUDY.
From 01/95 to 12/97 a pilot study demonstrated the feasibility of tandem ASCT in 43 patients with very unfavorable progressive HL. Our current protocol stratify progressive HL in 2 groups: group 1 included induction failure (IF) or early CR (< 12 mo) and disseminated (or previously irradiated site) relapse; patients received 2 course of salvage chemotherapy (IVA: 75% or MINE 25% when the total dose doxorubicin received exceeded 300 mg/m²) and non progressive patients achieved ASCT1 after CBV + mitoxantrone (30 mg/m²) then ASCT2 (cytarabine 6 g/m², melphalan 140mg/kg and total body irradiation at 12 Gy or busulfan 12 mg/kg). Group 2 patients with early or disseminated relapse received 3 courses of salvage chemotherapy and ASCT after BEAM regimen. The protocol activated in 01/98 has included 135 patients in first HL progression, we will present results on all 178 patients.

Group 1 N = 110
Group 2 N = 68

Mortality: 61% 59%
Histology at relapse: 70% 91%
Induction failure: 50% 0
Early relapse: 100% 22%
Extranodal relapse: 50% 25%
B-symptom: 45% 32%

Results: after salvage chemotherapy the response rate (CR + PR > 50%) was at 85% in group 1 and 94% in group 2. In group 1, 72% patients received the 2 ASCT with a response rate of 91%, the main reason not to receive ASCT was disease progression. In group 2, 94% of the patients received the ASCT and 2 refractory relapses received 2 ASCT with a response rate of 100%. 25 patients received IF RT after ASCT. In intent to treat analysis, the response rate was at 66% in group 1 (similar in IF or unfavorable relapse) and 94% in group 2. At 3 years, event free is at 50 and 75% and overall survival at 65 and 94% respectively in group 1 and 2.

A DOSE-INTENSIFIED MULTICENTER PHASE-II STUDY USING THE COLONIC HIGH-DOSE SEQUENTIAL CHEMOTHERAPY IN RELAPSED AND REFRACTORY HODGKIN'S AND AGGRESSIVE NON-HODGKIN'S LYMPHOMA
First Dept. of Med., University Hospital Cologne, 2 Med. Klinik, CTX Cotbus, Cotbus, 3Viroeh-Hospital, Humboldt University Berlin, 4Poliklinik Bonn, Bonn.
Combination chemotherapy can cure patients (ps) with Hodgkin's disease (HD) or Non-Hodgkin's lymphomas, but those with treatment failure or relapse still have a poor prognosis. High-dose chemotherapy (HDCT) with autologous stem cell support (ASCT) can improve the outcome of these ps as shown in the HL-R1 study of the GHSG/EBMT and the PARMA trial. We thus designed an intensified salvage program with a final unloading phase. Eligibility criteria include age 18-60 years, histologically proven primary progressive or relapsed HD and NHL. Treatment consists of two cycles DHAP; pts with PR or CR receive cyclophosphamide 4g/m², followed by PBSC harvest; methotrexate 8g/m² plus vincristine 1.4mg/m²; and etoposide 2g/m². The final myeloablative course is BEAM followed by ASCT.

161 ps (median age 36 years, range 18-65) with HD (n=103) or NHL (n=59) have been enrolled. So far 146 pts are available for the final evaluation (97 pts with HD, 49 pts with NHL). At 18 months of median follow-up (range 3-31 months) results are as follows: Response rate (RR) after DHAP: pts with HD: 87% (23% CR, 64% PR); pts with NHL: 69% (10% CR, 59%PR). RR at the final evaluation: pts with HD: 77% (66% CR, 9% PR), pts with NHL 49% (32% CR, 16% PR). PBSC harvest was successful in 96% of pts. Toxicity was tolerable. TFFT/OS for pts with HD are: early relapse 64%/87%; late relapse 68%/81%; PD: 30%/58%; multiple relapse 55%/88%. TFFT/OS for pts with NHL relapse: 42%/54%, PD 8%/22%.
We conclude that this regimen is feasible, tolerable and highly efficacious in very poor risk pts with aggressive NHL or HD. In pts with relapsed HD the GHSG/EBMT/EORTC is comparing this regimen in a prospective randomized study (activated 01/2001) with 2 cycles DHAP followed by BEAM (HD-R2 protocol).

ALLOGENEIC STEM CELL TRANSPLANTATION (SCT) WITH FLUDARABINE-BASED, LESS INTENSIVE CONDITIONING IN HIGH-RISK, RELAPSED/RESISTANT HODGKIN'S DISEASE (HD).
P. Anderlina, S. Acholonu, S. Giralt, N. Ueno, B. Andersson, I. Khouri, J. Romaguera, M. Rodriguez, F. Hagemeister, F. Cabanillas, R. Chalm. M.D.Anderson Cancer Center, Houston, USA.
Objective: To explore the feasibility of fludarabine (FDPD)-based conditioning followed by allogeneic SCT in high-risk, relapsed/resistant HD.
Methods: Allogeneic SCT following a fludarabine-based conditioning regimen in eighteen patients with advanced HD who failed multiple conventional treatments (median prior chemotherapy regimens: 5), radiation therapy (14/18) and a prior autologous SCT (14/18) was carried out. The median age was 30 years (18-52). Disease status at SCT was refractory relapse (n=6) and sensitive relapse (n=12). The median time to SCT after last autologous SCT was 8 months (I-52). The cell source was HLA-identical sibling (n=10) or matched unrelated donor marrow (MUD; n=8). The conditioning regimen was FDPD-cyclophosphamide + antibiomyctocene globulin (n=13), and FDPD-melphalan (FM; n=5).
Results: Myeloid recovery was prompt, with an absolute neutrophil count (ANC)≥500µL at day 11 (range 9-15). Median platelet recovery at 20µL/L was at day 10 (0-50), with seven patients never dropping below a platelet count of 20µL/L after conditioning. Chimerism and/or cytogenetic studies at day 30-100 indicate complete (100%) donor-derived engraftment in 7/10 evaluable siblings SCTs recipients and in 5/7 evaluable MUD SCT recipients. All FM recipients (MUDs; n=5) had 100% donor-derived engraftment. Day 100 transplant-related mortality (TRM) was 1/8 (%) overall. Acute GVHD occurred in 10/18 patients. Chronic GVHD was diagnosed in 6/17 evaluable patients (extensive in four). Seven patients have expired (non-relapse mortality n=3) and eleven are alive (six in remission) with a median follow-up of 7 months (2-51).
Conclusions: These preliminary data suggest that allogeneic SCT with fludarabine-based, less intensive conditioning is feasible in very high-risk, heavily pretreated HD patients, with acceptable engraftment and early TRK rates even in MUD SCTs.

FAVORABLE IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) ON RESPONSE TO THERAPY AND SURVIVAL IN PATIENTS WITH AIDS-RELATED HODGKIN'S DISEASE (ARHD).”
2Hospital Universitari Germans Trias i Pujol, 3Clinic, 4del Mar, 5Mataró and 6Sant Pau. Badalona, Barcelona, Spain.
Introduction. HAART has been associated with improvement of response to therapy and survival in AIDS-related systemic lymphomas, and non-Hodgkin primary CNS lymphomas. Its effect in patients with ARHD has not been evaluated.
Patients and methods. 45 patients with ARHD diagnosed in 3 hospitals from Catalonia, Spain, between 1989 and 2000. Twenty-six of patients were considered as Group 1: Patients without previous HAART when ARHD was diagnosed (n=33). Group 2: 2 patients receiving HAART at the time of ARHD diagnosis and subsequently (n=12).
Results. Patients from Group 1 had a lower frequency of HD as AIDS-defining event (22% vs. 38%, P<0.03) and a higher frequency of lymphocyte depletion (LD) histologic subtype (36% vs. 8%, P<0.01). No other epidemiological, clinical or biological differences were observed between the two groups. COPP or COPP/ABV were the most frequent chemotherapy schedules given to Group 1 patients (23 out of 34), whereas ABVD was the predominant chemotherapy for Group 2 (9 out of 12 cases). CR rate was 41% for Group 1 and 80% for Group 2 (P<0.01). Medians for disease-free survival (DFS) and overall survival (OS) were not achieved in patients from Group 2 and were 3 and 11 mo. for patients from Group 1 (P<0.002 and P<0.001, respectively). By multivariate analyses HAART therapy was the only variable with favorable influence on CR attainment (OR: 3.3, 95%CI: 1.2-23.2), whereas HAART (as protective) and LD subtype influenced on DFS (OR: 11.9 [2.0-120] and 6.5 [1.04-14, respectively], and HAART (as protective) and hypoproliferative OR: 8.6 [2.3-32.7] and 10.6 [2.3-46.4], respectively) showed influence on OS.
Conclusions. HAART is associated with improvement of response to therapy and survival in patients with AIDS-related Hodgkin’s lymphoma.
Supported in part by Grant P-EF-01 from Fundación Internacional José Carreras.
The management of Hodgkin’s disease during the second trimester of pregnancy

E Lampka, J Meder, J Tajer, A Kawecki, J Walewski, B Brzeska
Memorial Cancer Center - Institute of Oncology, Warsaw, Poland

Aim: To evaluate clinical features and outcome of pregnant patients with Hodgkin’s disease treated by a single institution. Based on our experience we have discussed the very big problem of staging and of treatment Hodgkin’s disease during second trimester of pregnancy. Patients and methods: 21 pregnant patients with Hodgkin’s disease were treated between 1987 and 2001. Characteristics of patients: age 17-37 (range 29), trimester of pregnancy: I - II, I-II, III-III, clinical stage: I - II, II-III, III-IV, B symptoms: 7, histology: NS-I, NS-II, MC-III. Treatment: 1 trimester-therapeutic abortion, II trimester - method “watch and wait”. Second trimester: 4 patients - involved field RT-total dose 20-44 Gy (median 35 Gy). The supradiaphragmatic RT with fetus protection in these patients applied between 23-36 weeks. The thermoluminescent dosimetry was applied. 100 and individual blocks of the abdomen were used. The dose of the fetus was estimated every day -total dose 15,7-19,19 Gy. After delivery all 4 patients were treated with chemotherapy: 1-LOPP, 1-ABVD, 2-MOPP/ABV. 5 women were treated with chemotherapy regimen EVA 3-24 hours 3 to 4 cycles. After delivery involved field or mantle field RT (total dose 35-45 Gy). Results: all the patients: after treatment 21 complete remission was observed from 2-144 months, 4 patients had relapsed from 3 months to 6 years after first treatment, 3 women were treated of second line chemotherapies and 1 of them died and 1 is during the treatment. Third woman received the treatment of chemotherapy and PBSC. 17 patients delivered full-term (36-39 weeks) normal infants. 16 children are alive. All of the children are in good health without late complications connected with previous chemotherapy and irradiation. 1 boy died 6 days after delivery-respiratory distress syndrome. Conclusions: Treatment requires individualization to insure that the patient will be cured and the fetus protected.

SECOND MALIGNANCIES IN MANAGING HODGKIN’S DISEASE

Katalin Keresztes, Szőfia Mátéföy, Csilla András, Árpád líls
3rd Dept. of Internal Medicine, Medical and Health Science Center, University of Debrecen, Hungary

The aim of the study: to analyse the incidence of second malignant neoplasms (SMN) in patients treated for Hodgkin’s disease.

Patients and methods: Since 1 January 1967, 534 patients have received primary treatment for Hodgkin’s disease and 470 cases have proved to be adequate for data analysis as regards to the development of SMN.

Results: A total of 34 cases (7,2%), solid neoplasms were diagnosed in 26 cases (5,5%), lung neoplasms had the greatest incidence (11,26), hematologic malignancies were detected in 8 cases (1,7%) and non-Hodgkin’s lymphoma was found in 5/8 cases. The mean age of patients with solid neoplasms was 38,1 years (18-59 years) at the diagnosis of Hodgkin’s disease and the length of time between the diagnosis of Hodgkin’s disease and the time of diagnosis of secondary malignant tumours was 13,5 years (1-33 years). The mean age of patients with hematologic malignancies was 45 years (17-64 years), the latency period was 3,2 years (9 months-12 years). The therapies employed prior to the development of solid neoplasms include: irradiation in 6 cases, chemotherapy in 8 and combined therapy in 12 cases. Out of the 20 cases of chemotherapy, CV/O/PP and its variants were used in 17 cases. Prior to the development of hematologic malignancies, 5 patients had received chemotherapy, 3 combined therapy and 7 patients CV/O/PP and its variants.

Conclusions: The incidence of SMNs, especially as regards to hematologic malignancies, was found lower in our patients as compared to literary data. This can be explained by the less intensive therapeutic techniques employed earlier as well as by shorter survival periods. As a result of better therapeutic management, the chance of long term survivals have increased and we should make every effort to avoid late complications such as second malignant neoplasms when planning therapeutic strategies.

SEmen cyroPREServation, utilisation and reproductive OUTCOME IN men treated FOR Hodgkin’s diseasE. FH Blackall1, AD Atkinson2, MB Mayya1, WD Ryder1, G Home1, DR Brison1, BA Lieberman2, JA Radford3, CRC Department of Medical Oncology, Christie Hospital, and 2 Department of Reproductive Medicine, St.Mary’s Hospital, Manchester, UK.

Infertility is a common late effect of treatment for Hodgkin’s disease and is particularly important since most patients are young adults at diagnosis. Currently, semen cryopreservation is the only technique available to preserve reproductive potential in men but little information exists as to the benefit of this policy.

A cohort of 122 men who presented to this regional Cancer Centre with newly diagnosed Hodgkin’s disease between 1978 and 1990 were studied. Patient demographics were obtained from the Manchester Lymphoma Group database and matched with data concerning pre-treatment semen analysis, semen storage, post- treatment utilisation and reproductive outcome held at St. Mary's Hospital. All patients received MVPP or CHVPP/EVA hybrid chemotherapy (CT) which produce equivalent gonadal toxicity (J Clin Oncol 1995;13:134-139).

Median age for the group was 24 years (16-44). 81 (66%) had semen quality within the normal range by WHO criteria, 25 were oligospermic and 5 were azoospermic. Semen from 115 men was cryopreserved. Following treatment, 74 men had semen analysis performed at least once (median 2, range 1-7); at the first analysis a median of 2.9 years after completion of CT, 68 (92%) were oligospermic, 4 (5%) were severely oligospermic and 2 had a normal sperm concentration (both had received only 3 cycles of MVPP). A degree of recovery of spermatogenesis was ultimately detected in 13 (17%) men. After a median follow-up time of 10.1 years for non-utilizers, 33 men have utilized stored semen (actuarial rate 27%) and 10 patients have become pregnant resulting in 11 live births (8 singletons and 3 triplets, live birth rate of 27%) and 2 terminations of sequential pregnancies in the same woman for fetal malformation. Actuarial 10 years rate of destruction of semen before death or utilisation and death before utilisation are 15% and 13% respectively.

This retrospective cohort study demonstrates that recovery of spermatogenesis is unusual after MVPP or CHVPP/EVA and approximately a quarter of men utilizing cryopreserved semen after treatment for Hodgkin’s disease obtain a live birth.