7. Hodgkin’s Disease

LEUKOPENIA PROGNOSIS DURING RADIATION- AND CHEMOTHERAPY IN PRIMARY PATIENTS WITH HODGKIN’S DISEASE S.D. Ivanov, V.A.Yamshchikov, N.V.Ilyin, A.A.Akimov and I.Ye. Vorobtsova. Central Research Institute for Roentgenology and Radiology, St.Petersburg, Russia

Introduction: Leukopenia represents one of the major risk factors for the development of infections among patients with Hodgkin’s disease (HD) following regimes of intensive treatment. The purpose of our study was to elaborate a new method for leukopenia prognosis by in vitro determination of blood leukocytes DNA content changes after test-irradiation before the patients treatment start.

Methods: Primary patients with II-II1 stages HD were treated at the 15 MeV linear accelerator by mantle and Y-inverted extended fields irradiation with usual fractionation to total dose 40 Gy, or at routine chemotherapeutic (CT) course (COPP or COPP-ABVD), and their vein blood was analyzed. Blood samples (1.5-2.0 ml) of 25 patients were irradiated in vitro by “Luch-1” gamma-unit (60Co) with 2 Gy dose, and were then incubated at 37°C for 3 hrs. The DNA concentration was determined with use of 4,6-diamidino-2-phenylindol (DAPI). A ratio of the DNA quantity per leukocyte (D/L) in control (nonirradiated) to irradiated probe was presented as an index S/Ci.

Results: Retrospective analysis of data during radiation therapy (RT) allowed to reveal 2 groups of patients. The 1st group of patients, having blood leukocyte level above 3 x 10^9 cells/l during RT, revealed the D/L decrease after the middle of treatment course only. The 2nd group patients, having at the end of RT several leukopenia, showed approximately 2 times decrease of the D/L after the 1st irradiation. The blood leukocyte amount was at minimal level from 6 to 33 days among patients treated by RT or CT. Correlation analysis evidenced that the elaborated S-parameter correlated with a discretic number only (r=0.05), but not with other chromosomal injuries. The in vitro determined S-values correlated with the leukocyte nadir positively during polychemotherapy (R= 0.644; p<0.05), or negatively during RT (R=-0.53; p<0.01).

Conclusions: The elaborated index may be used for individual leukopenia prognosis among primary patients with HD as a short-term and sensitive test before the treatment start to choose an adequate tactic of the treatment, and corresponding supportive care.


Objective of the study was to elucidate possible correlations between HLA antigens and HD prognosis (relapse or remission). As we have previously shown HD is characterized by increasing of Cw 7 and DRB1*11 frequencies (RR=3,3 and 5,06 correspondently) decreasing of DRB1*01 and 07 frequencies (RR=0,11 and 0,16 correspondently) [Zaretskyaya et al. 1998]. The DRB1*11 and Cw 7- frequencies in patients with relapse were > 5 years (n=53, birelapae (n=18) c) general pool=n=71) are statistically equal. These genes, being the structures of HD - predisposition, have not influenced on HD outcome. In remission - group the frequency of DRB1*01 was increased (20,8x v.s.2,1 % in pool); so this genetic structure is predisposing factor for remission. Also there was the accumulation of A 28-, B 5- . B 13 -carriers as compared of pool group. In relapse-group there was the accumulation of A 28-, B 5-, B 13 - carriers. So some HLA - specificities are the prognostic factors for HD outcome.


We report the case of a 26-year old man who suffered from generalized Langerhans cell histiocytosis (LCH) after having been treated for paragranuloma stage III BE, in cooperation with German Hodgkin’s Disease Study Group. Chemotherapy BEACOPP escalated + radiotherapy induced complete remission.

14 months later splenectomy was performed because of spontaneous rupture. Splenic infiltration was classified as Langerhans cell histiocytosis of the basis of the morphological features with presence of CD1a and S-100 protein expressing histocytes. Clinically, 3 weeks later, the patient presented with recurrent fever and fatigue. Imaging methods revealed abdominal lymphanphadopathy, bone marrow infiltration, infiltration of the liver and bones (vertebrae Th2, Th3).

The patient was treated by the protocol of Austria/ German Group for LCH: DAL - TX 83/90 (LCH II Study: initial treatment - PDN, VP16 and VBL) followed by the paliative analgetic radiotherapy of affected bones.

In spite of the therapy, the patient died of diffuse massive gastric bleeding 2 years after onset of Hodgkin’s disease (HD) and 10 weeks after the manifestation of LCH. Necropsy did not reveal HD. Residual LCH was found in cervical, thoracic and abdominal lymph nodes as well as in bone marrow. Pseudolobar pneumonia was present.

LCH is associated more frequently than expected with malignant neoplasms. Lymph node involvement by LCH in HD was already reported. Generalized LCH secondary to HD is a very rare complication.

7. Hodgkin’s Disease

151
Advanced stage Hodgkin's disease (HD): preliminary data of HD 94 protocol (ABVD vs ABVP/OPP).

Introduction: At the moment, patients (pts) affected by advanced stage HD achieve acceptable results in terms of overall survival (OS) and relapse free survival (RFS); however, these pts may have long-term complications particularly in terms of cardiac and pulmonary toxicity which compromise their quality of life. In order to reduce long-term toxicity, in January 1995 we started a prospective randomized trial comparing a well known scheme of chemotherapy ABVD with an alternating new scheme ABVD/OPP (Vinirucin 1.5 mg/m² d1, 8, 15, Procarbazine 100 mg/m² d1-21, Prednisolone 40 mg/m² qd d1-21).

Results: Of the 54 pts enrolled in arm A (ABVD), 51 pts were evaluable for response (3 pts are still receiving chemotherapy). After the 6 cycles of ABVD regimen, 50 pts (98%) achieved CR and 1 patient only reached PR (he is still alive with disease). Of the 50 pts enrolled in arm B (ABVP/OPP), 48 pts were evaluable for response (2 pts are still receiving chemotherapy). After 6 cycles of ABVP/OPP regimen, 44 pts (92%) achieved CR, 3 pts reached refractory and one patient, 63 years old, died of myocardial infarction. Of the 3 pts refractory, one patient died of HD, one patient is still in CR and the latter is still receiving chemotherapy. In both groups acute toxicity was acceptable excluding the patient who died in arm B for cardiac toxicity. All pts, during chemotherapy, used a cold cap, to avoid alopecia. With regard to chronic toxicity, in arm B, one patient, 68 years old, had a delayed cardiomyopathy 24 months after therapy; in arm A 16 pts of 60 developed a pulmonary fibrosis, whereas, in arm B, 8%, OS and RFS were 100% and 93% respectively and were 100% and 93% respectively in arm B (range 1.44 months).

Conclusions: Results, at a median follow-up of 24 months, show that both chemotherapy regimens are equally effective in advanced stage HD in terms of response and toxicity, excluding pulmonary fibrosis (16% in arm A and 8% in arm B). On the other hand, a longer follow-up is required to confirm these data.

RADIOThERAPY ALONE AS THE TREATMENT OF CLINICALLY STAGED (CS) IIA, NON BULKY, HODGKIN'S DISEASE (HD). A SINGLE INSTITUTION EXPERIENCE ON 487 PATIENTS.

Depl. of Radiotherapy and Nuclear Medicine of Padua, Italy.

Purpose: The aim of this study was to analyse the possibility of omitting laparotomy in selected pts CS non bulky-IIA HD treated with radiotherapy alone.

Methods: From January '85 to January '98, 67 previously untreated pts with HD underwent clinical staging procedures consisting of history, physical examination, routine haematological tests, chest X-ray, total body CT scan, bicipital lymphangiography, bone marrow biopsy and laparoscopy with multiple random spleen and liver biopsies. They were 29 males and 38 females, median age 36 yrs (range 14-72). The stage was IA in 31 pts and II A in 36, histology was SN in 41 pts, PL in 14 and CM in 12. Of the 36 IIA stage pts, 24 showed an involvement of 2 lymphoid regions, 11 of 3 regions and 1 of 4 regions. All pts were treated with radiotherapy alone for a total dose of 35.6 Gy in 22 fractions. Of the 36 IIA stage pts, 33 were treated with subtotal lymphoid irradiation (STLI) (mantle plus paracostal and spleen field) and 3 with a mantle field alone, whereas 21 IIA stage pts, 17 were treated with STL, 5 with mantle field, 1 (72 yr old pt) with an involved field and 4 with an inverted Y plus spleen field. After a medium follow-up of 89 mths (min 12, max 181, median 87), 83% (97%) are still alive without evidence of disease 7 pts (10.4%) released stage, 3,11,12,15,28,29 and 48 mths after the diagnosis. Initially the stage of these pts was IA in 3 and II A in 4, while the histology was SN in 5, PL in 1 and CM in 1. We did not find failures (48 mths after the diagnosis). All sites of relapse: were bone (2 pts), bone marrow plus liver (2 pts), axillary nodes (1 p) and inter-mammary chain nodes (1 p). All relapsed pts had previously undergone STLI. At relapse, 5 pts received chemotherapy plus radiotherapy and 1 radiotherapy alone. Only 7 out of 7 pts obtained a complete second remission still lasting after 12, 53, 55, 83, 88 mths respectively, while 2 pts (2.9%) died due to progressive disease respectively 3 and 5 mths after relapse.

Conclusions: Our data suggest that a well defined group of pts with early stage HD, who undergo an accurate clinical staging procedure, can be effectively treated with radiotherapy alone avoiding laparoscopy. The role of laparoscopy in detecting abdominal disease in these pts will be discussed.
TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED FACTORS TRAF2, TRAF3 AND TRAF5 IN HODGKIN'S DISEASE

Tingyu G. G., N., Xun, N., Redor M., Gordon P., Padilla E., Boischel B., Division of Clinical Pathology, University Hospital Geneva, Switzerland, *Institute of Pathology, University of Basel, Switzerland, **Institute of Pathology, Locarno, Switzerland.

Introduction: TNF receptor-associated factors (TRAFs) have emerged as intracellular signal transducers for some members of the TNF superfamily. TRAF2, and TRAF5 are implicated in NF-κB activation, but not that of TRAF3. With the exception of TRAF4, all other TRAFs (TRAF1-6) have been shown to interact directly with the non-death domain of CD90 and CD40. Furthermore TRAF2, and TRAF5 interact with the latent infection membrane protein 1 (LMP1), the transforming protein of the Epstein-Barr virus (EBV) Hodgkin's disease (HD) in Western countries is associated with EBV in around 50% of the cases. The malignant Hodgkin and Reed-Sternberg cells (HRS) harbour the virus in its latent form, characterized phenotypically by the expression of EBER, an early viral RNA and LMP2. Among other factors the RS cells elaborate cytokines and express members of TNF-receptor family, including CD30 and CD40.

Aim of the study: We investigated the expression of TRAF2, TRAF3 and TRAF5 in cell lines containing or not the herpes virus HHV8 and/or EBV (HHV4), respectively. Second, we determined the expression of TRAF2, 3 and 5 and EBY association in different types HD.

Materials and Methods: Immunohistochemistry (IHC) Cytoscopy of the following lymphoma cell lines were performed: BC (EBV+/HHV8+), BC-2 (EBV+HHV8+), BC-3 (EBV-,HHV8+) and the Burkitt cell line BJAB (EBV-/HHV8-). The cells were processed for immunostaining. Formalin fixed, paraaffin-embedded tissue of different types of HD were routinely stained with HE and Giemsa. A standard panel of IHC, included antibodies against CD15, CD30, CD20, CD3, CD40, EM and LMP (Dako, Copenhagen) A streptavidin-biotin-HRP (Dako) based detection method was used for TRAF2, 3 and 5 (Santa Cruz, California) immunohistochemistry. Hybridization of very mRNA of EBV, EBER (Dako, Copenhagen) was carried out on all the HD cells.

Results: Cell lines TRAF2 was expressed in BJAB cells, and weakly in fresh cells of BC-1. TRAF3 and TRAF5 were equally expressed in all cell lines, with strongest signals in the large malignant HHVS negative Burkitt cell line BJAB. HD cases: In all the cases tested, the HRS-cells stained for CD15 and CD40. TRAF3 was variably expressed by EBV negative HRS-cells in 20% of the cases independently of the histological type. Only few, EBV negative cases showed very weakly, unevenly distributed signals for TRAF5. TRAF2 was not expressed HRS-cells. Conclusion: TRAF2 is the major TNF receptor-associated factor expressed by HD cells. Moreover, TRAF3 expression was stronger in EBV-negative HD cells.

COMPARISON OF TWO PROGNOSTIC SYSTEMS - V. DIELH, AND J.-M. ANDRIEU'S SYSTEMS - AMONG 180 HOMOGEOUNS TREATED PATIENTS WITH HODGKIN'S DISEASE.


Maladies du Sang - CHU Amiens & Hospital Larraze - Paris - France.

We treated 180 patients (pts) - 106 males and 74 females - aged between 15 and 75 years (mean age 45 years) with abdominal or axillary lymph nodes, defined as 'adapted infiltration', according to the HI and HI 90 trials. Clinical stages were IIb, II A, II B, III A, III B and IV.

We used 12 toxic deaths, 13 failures 165 CR (92%) and 115 with a 13 years median follow-up time, 20 relapses and 33 deaths of which 2 ARDS, 5 mycobacterial infections, 1 CVA, 3 second tumors, 2 NHL and 1 AML. The 12-year survival rate is 77 ± 4% with 2 later deaths (NHL and mycobacterial infection at 168th and 196th month). In opposite DFS curve shows a 10th month at 79 ± 3% level. Among the 7 prognostic factors identified by Dihel and all, (NEJM, 1998, 150-154), age and sex are without prognostic value looking DFS and value of stage IV disease is borderline (p=0.07). The Cox model keeps anemia, hyperlymphocytosis and lymphoepupa. This system can define 3 prognostic groups: 95 pts with score 1 ≤ 68 pts with score 2 or 3 and 17 pts with ≥ 4. DFS rates are at 88, 70 and 65% respectively (p=0.003). The same computation among the 98 'advanced' stages as defined by Dihel and all keeps anemia and age in multivariate analysis but DFS rates of the 3 prognostic groups are not statistically different. 76% (30 pts), 65% (52 pts) and 63% (16 pts).

Andrieu's system (Ann Oncol 1998, 19, 2019-2135) is based on 3 parameters:
- the number of involved area according to Aron system: 1 or 2 vs 3 or 4 vs 5
- the mediastinal mass ratio from 0 to 0.32 to 0.33 to 40 to 44 vs 45 and 46
- the number of involved viscera: 0 vs 1 vs 2.

This system can identify 1 groups with well-balanced rates and a very different prognostic when looking at DFS (p=0.0001) and at 12 year overall survival (p=3.000). This system is very effective among the 98 Dihel's 'advanced' stages for DFS and survival (p=0.0001) and also effective among the 133 stages for DFS and survival (p=0.0001 for DFS & 0.005 for survival) when the LORCT system is only significant for DFS (p=0.02).

APOPTOSIS AND PROLIFERATION IN REFRACTORY HODGKIN'S DISEASE

S. Jankovic, V. Cemekovic-Martirovic, A. Bogdanovic, B. Mihajlovic, G. Milivojovic, R. Janicij-Nedeljkovic, M. Colovic, M. Petrovic.

Institute of Hematology, *Institute of Pathology, Clinic Center of Serbia, Belgrade, Yugoslavia.

Introduction: Proposed prognostic variables in Hodgkin's disease (HD) often failed to recognize primary refractory cases (PRHD) and those with early relapse within one year since diagnosis (ERHD). We tried to determine whether the expression of apoptotic and proliferative gene product proteins differs in patients with PRHD and ERHD and those with long lasting complete remissions (CRUD).

Methods: Ten patients with PR/ERHD and seven pts with long lasting CR were diagnosed as HD nodular sclerosis type. Both groups were matched for age, sex and clinical characteristics. We investigated proposed prognostic variables (nodular sclerosis subgroups, ESR, hemoglobin level, serum album level, serum LDV level, generalized purulent, absolute lymphocyte count, number of involved sites and tumor burden), and the immunophenotypes (CD15, CD30, CD79a, Epstein-Barr virus presence and the expression of the PCNA, Ki-67, p53, CD40, bcl-2, bax, cyclin D1, and mdr-1 gene products. Immunophenotype, EBV presence and proliferative assessment were done by immunohistochemical Streptavidin-biotin-alkaline-phosphatase method. The results of each group were compared using Kruskal-Wallis ANOVA test.

Results: We have found no statistically significant difference in any of the proposed prognostic variables between two analyzed groups, neither difference in immunophenotype nor EBV presence. Statistically significant difference (p<0.05) was noticed in the level of expression of Ki-67, CD74, bcl-2 and mdr-1 with higher expression of all four in PR/ERHD pts. This group also had higher histological grade.

Conclusion: Our results suggest that high growth fraction and suppressed apoptosis combined with high level of mdr-1 expression can predict poor clinical outcome and resistance to therapy in patients with HD nodular sclerosis type at presentation.

STANFORD V REGIMEN IN BULKY OR ADVANCED-STAGE HODGKIN DISEASE


Department of Hematology, Radiotheraphy and Pathology, University Hospital Gasthuisberg, Leuven, Belgium.

Introduction: The Stanford V regimen was designed to short treatment duration and significantly reduce cumulative doses of alkylating agents, doxorubicin and bleomycin, while maintaining dose intensity (DI) in Hodgkin's Disease (HD). (J Clin Oncol 13, 1080-1088, 1995.) The goal was to decrease acute morbidity and risks for late complications while maintaining efficacy.

Methods: Since February 1997, 26 previously untreated patients (15 males, 11 females, median age 43.5 years) with stage II HD with bulky mediastinal involvement (≥7 cm), stage III B (n=8) and stage IV (n=11) received this regimen for twelve weeks. Consolidative radiotherapy was given to 23 patients to sites of original bulky disease or radiographic abnormalities that persisted after chemotherapy.

Results: Twenty-one patients (81%) achieved a complete remission (CR) and all remain in CR a median of 6 months following therapy. No patient had disease progression during therapy but 5 patients (19%) failed to reach a CR and have subsequently developed progressive disease. All patients are alive with a median follow-up duration of 13 months. Toxicity: Thirty-one percent of patients had a 1-week delay due to myelosuppression and eleven percent had more than one delay during the twelve weeks. There was only one hospitalisation for fever and neutropenia, and no documented infections. Forty-two percent of patients had at least one episode of grade 4 neutropenia. Neurologic side-effects were mainly obitation and parotidis and developed in 16 (62%) of patients and resolved after therapy. There were two hospitalisations due to severe obitation and ileus, that resolved rapidly.

The median actual relater DI (ratio of actual to expected dose in milligrams/m² per 12 weeks) was >0.98 for each of the individual drugs (range 0.96 to 1.00). Fourteen patients (54%) who required a dose reduction or delay were given G-CSF throughout the remainder of the regimen.

Conclusion: The Stanford V regimen proved to be a well-tolerated regimen and a very high DI was maintained in all patients. The follow up period in this small group of patients is relatively short, but our preliminary results compares well with standard regimens. It does not, however, mirror the excellent results from Stanford University. The fact that there were partial remissions and a very short time to subsequent progression of disease in the 5 patients that failed to reach CR, suggests that intensification of treatment, a longer duration of treatment or high-dose consolidation are indicated in this subset of patients.

7. Hodgkin's Disease
HYBRID-NOU CHEMOTHERAPY FOR ADVANCED HODGKIN'S DISEASE

National Cancer Institute, Bratislava, Slovakia

A modified regimen of the original Vancouver hybrid was developed in our institution for the treatment of advanced Hodgkin's disease (HD). The main purpose was to reduce long-term toxicity caused by mechloethamine.

From February 1991 to October 1996, 131 patients with either newly diagnosed advanced HD or with relapsed disease after radiotherapy were included. The treatment schedule was identical to MOPP/ABV hybrid regimen, except of mechloethamine, which was omitted and replaced by lomustine (40mg/m² p.o. d1). Responders received a minimum of 6 and a maximum of 9 cycles. Consolidative involved field radiotherapy was applied to the sites of initial bulky masses (>5cm) as well as to persistent radiological abnormalities after chemotherapy. Median age was 27 years, 76 patients had stage I/I, 40 stage IV and 15 pts. had stage II/III with unfavorable prognostic features. B symptoms were present in 73 patients.

With a median follow-up of 58 months, the 5-year overall survival rate was 87%, and failure-free survival was 76%. There were 3 toxic deaths (septic shock-1 pt., fatal bleeding-1 pt., unknown cause-1 pt.). Toxicities (WHO grade III/IV) were observed in 66 cycles (7%), mostly leukopenia and infectious toxicity. There have been no secondary malignancies.

It appears that Hybrid-NOU is a safe and efficient regimen for advanced HD; however, substantial subset of patients who are not cured with current standard chemotherapy require new treatment strategies.

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For patients with stage I/II, non-bulky disease received mantle radiation therapy (RT) alone, 2 additional cases have received combined chemotherapy & regional RT. All other stages were given chemotherapy treatment. Patients with bulky disease (12 cases) were given regional radiotherapy in addition to chemotherapy. Furthermore, 9 patients with advanced stage (non-bulky disease) were given additional regional RT for residual disease. The most commonly used combination chemotherapy regimens were: MOPP/ABVD (27.6%), MOPP (15.5%) and ABVD (13.5%), and others. Up to the period of December 1998, three cases (5.7%) of relapse were documented. No Toxic death has occurred. Complications were poorly documented.

Conclusions: RCCO provides integrated approach to patients with HD, resulting in a high rate of response. The recommendations of the analysis are as follows: HL patients need a long follow-up to determine the actual cure rate. There is unnecessary use of regional RT in some cases as this might expose the patients for unnecessary long term complications. Finally, proper documentations are required for the treatment complications.

CLINICAL STAGE (CS) II OF HODGKIN'S DISEASE (HD) - TREATMENT WITH CVPP PLUS RADIOTherapy. SINGLE INSTITUTE EXPERIENCES

Demina E., Joureaa T., Tumjan G., Kondratjeva N.
Cancer Research Centre (CRC), Moscow, Russia

Introduction: The result of local stages HD combined modality therapy is good. However long-term toxicity decreases event free survival in a group of patients (pts). So the optimal capacity treatment program is discussed.

Methods: Since 1980 to 1995 159 previously untreated pts with CS II of HD received combined modality therapy. The median follow-up was 80 mes (range 3-186 mos). There were three groups: 41 pts with "good" prognosis (NS and LP histological subtypes, age<40, no more 2 lymphoid areas, B- mpt=<ESR<30 and no B-symp<ESR<50) and 11 pts with "poor" prognosis (all other patients with CS II of HD). In "poor" prognosis group treatment consisted of 3 CVPP (cyclophosphamide, vincristine, procarbazan, prednisone) + extended-field irradiation (SF) in dose 36 Gy + 3 CVPP = 57 pts. And 3 CVPP + involved-field irradiation (IF) in dose in dose 36 Gy + 2 CVPP = 61pts. Treatment was reduced to 2 CVPP + IF in dose 40 Gy + 2 CVPP in "good" prognosis group.

Results: 3CVPP+IF=3CVPP 3CVPP+IF=3CVPP 3CVPP+IF=3CVPP CR-rate 93% 95% 98%

6-year DFS-rate 85% 84% 94%

PFTT-rate 81% 81% 88%

EFS-rate 73% 81% 87%

OS-rate 94% 97% 100%

CR-Complete remission, PFTT=progression free survival, EFS= event free survival, OS=overall survival.

Secondary malignancies (SM) developed in 4 pts (3%): CR urti in 1 case, gastric non-Hodgkin's lymphoma in 1 and thyroid Cr in 2 (both in the irradiated area), SM decreased EFS to 75% in group of pts with 3CVPP+IF=3CVPP treatment.

Conclusions: The involved-field irradiation in combined modality therapy for pts. with CS II of HD and "poor" prognosis didn't make the results worse and may be sufficiently. For pts. with CS II of HD and "good" prognosis the treatment program 2 CVPP + IF = 2 CVPP is enough for good results.

RECOMBINANT AND HUMANIZED IMMUNOTOXINS FOR THE TREATMENT OF HODGKIN'S DISEASE: EXPERIMENTAL DATA

S. Barth, A. Engert
Laboratory of Immunotherapy, University Hospital of Cologne, Germany

Introduction: Results of ongoing phase I/II clinical trials with chemically linked immunotoxins (ITs) indicate efficacy in particular against leukemia and lymphoma. Thus, ITs might be useful to eliminate residual tumor cells possibly resulting in reduced number of relapses. Recombinant DNA technology makes it possible to genetically fuse coding regions of V genes or cytoplasmic to modified toxin domains. These recombinant immunotoxins can easily be manipulated to increase the cytotoxic potency or affinity by i.e. site-directed mutagenesis and produced in large quantities.

Methods: Binding single-chain variable fragments (scFv) expressed as chimeric fusion proteins on the surface of filamentous bacteriophages were selected on Hodgkin-derived cell lines. This technique was also used to create a new humanized anti-CD30 scFv which exhibits similar binding to the CD30 antigen when compared to its murine predecessor, scFvs were then inserted into a newly constructed pET-based bacterial expression vector (pBM1.1) and thus fused to a deletion mutant of Pseudomonas exotoxin.

Results: Anti-CD25(scFv)-ETA’ and anti-CD30(scFv)-ETA’ were isolated from Ecoli periplasm and purified by metal chelate affinity and size exclusion chromatography. All fusiontoxins produced showed specific cytotoxicity against Hodgkin lymphoma cell lines as documented by competitive assays. In addition, these constructs were highly efficient in the treatment of disseminated human Hodgkin's lymphoma in SCID mice.

Conclusions: These in vivo data will be presented for the first time indicating a possible clinical impact in patients with relapsed CD30-positive lymphoma.

HODGKIN'S LYMPHOMA IN KUWAIT: CLINICAL FEATURES & TREATMENT OUTCOME

S. Al Sharshiani, Shafika Al Awadi, N. A. Alabbas. Faculty of Medicine, Health Sciences Center, Kuwait University & Kuwait Cancer Research, Ministry of Health, Government of Kuwait.

AIM: The purpose of the study is to analyze all cases of Hodgkin's lymphoma (HL) which have been diagnosed and treated during the period of January 1992 and December 1995 at the Kuwait Cancer Control Center (KCCC), Ministry of Health, Government of Kuwait.

Methods: A retrospective analysis of HL cases which were diagnosed between January 1992 and December 1995 and followed up until December 1998. Standardized format was developed for data collection.

Results: 58 cases were analyzed. Mean age 27.4 years (+/- 17.3) (range: 5-62 yr). There were 31(53.5%) males and 27(47.5%) females. 27(46%) were Kuwaiti nationals, 28(49.1%) Arab non-Kuwaitis and 3(4.3%) of other nationalities. Histology was as follows: nodular sclerosis 41.4%, mixed cellular 39.7%, lymphocytic predominance 13.8% and lymphocytic depletion 3.4%. One case only with unidentified histology. Of the 58 cases 4 patients (5.9%) underwent staging laparotomy. The majority (80.9%) of cases are early stages (Stage I-II), 27.6% have bulky disease, 6% have extra-nodal involvement and 34.5% have B-symptoms.

Tentative outcome: Treatment per stage shown below.

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2 patients with stage IA, non-bulky disease received mantle radiation therapy (RT) alone, 2 additional cases have received combined chemotherapy & regional RT. All other stages were given chemotherapy treatment. Patients with bulky disease (12 cases) were given regional radiotherapy in addition to chemotherapy. Furthermore, 9 patients with advanced stage (non-bulky disease) were given additional regional RT for residual disease. The most commonly used combination chemotherapy regimens were: MOPP/ABVD (27.6%), MOPP (15.5%) and ABVD (13.8%), and others. Up to the period of December 1998, three cases (5.7%) of relapse were documented. No Toxic death has occurred. Complications were poorly documented.

Conclusions: KCCC provides integrated approach to patients with HL, resulting in a high rate of response. The recommendations of the analysis are as follows: HL patients need a long follow-up to determine the actual cure rate. There is unnecessary use of regional RT in some cases as this might expose the patients for unnecessary long term complications. Finally, proper documentations are required for the treatment complications.
CLINICAL TRIALS WITH AN ANTI-CD25 RICIN A-CHAIN IMMUNOTOXIN IN REFRACORY HODGKIN’S LYMPHOMA

R. Schnell1, E. Vietet1, J. Schnieder2, V. Gehricke, K. Heil1, P. Horschmann1, S. Barth1, V. Dietl1 and A. Engert1
1) Klinik I für Innere Medizin der Universität zu Köln, Germany
2) Cancer Immunobiology Center & Dpt of Microbiology, Texas, USA
3) Institut für Pathologie der Universität zu Köln, Germany

Introduction: Immunotoxins (ITs) consisting of a binding and toxin component were developed as a new class of biological anti-tumor agents to improve adjuvant therapy. Hodgkin’s lymphoma (HL) has been demonstrated to be an excellent target for ITs due to expression of lymphocyte activation markers such as CD25 and CD30. The anti-CD25 RFT5.dga was constructed by linking the Moab RFT5 to deglycosylated ricin A-chain and was evaluated for its clinical use in a phase I/II trial. The IT was administered every second day (1-3.5-7) i.v. over 4 hours.

Methods: In the phase I trial we treated reactory HL patients with escalating concentrations of the IT to evaluate the maximum tolerated dose (MTD). Objectives were documentation of dose limiting toxicities, evaluation of pharmacokinetic parameters and immune response to the IT.

Results: The MTD in these patients was 15 mg/m². Dose-limiting toxicities were primarily due to vascular leak syndrome (VLS) with edema, tachycardia, hypotension, weakness and myalgia. Measurement of serum levels demonstrated a Cmax of 0.9-7.9 mg/ml, half-life varied from 4-10.5 h. More than 90% of patients developed human anti mouse and/or anti-ricin antibodies. 16/18 patients in the phase II received the IT twice or more cycles and thus were evaluable for clinical response. These included two partial remissions, one minor response, and five stable diseases. The median tumor progression of responding patients was 142 days. The median survival time of all patients was 742 days.

Conclusions: RFT5.dga is well tolerated in a dosage of 15 mg/m² and is of clinical efficacy in a group of heavily pretreated reactory patients. Future trials should aim on the use of a combination of two or more ITs in patients with minimal residual disease.

IMMUNOHISTOCHEMICAL EXPRESSION OF p53, Waf1/p21 Rb AND Ki-67 (MIB-1) PROTEINS IN HODGKIN’S DISEASE (LD)

Departments of Pathology of the University Hospital, «Venizeliono Hospital of Heraklion, Crete and «Evangelismos Hospital of Athens, Greece.
Departments of Hematology of the University Hospital and «Venizeliono Hospital of Heraklion, Crete, Greece.
Department of Pediatric Hematology/Oncolesy, University Hospital of Heraklion, Crete, Greece.

Introduction: We studied the expression of p53 and p53 inducible Waf1 protein in H.D in correlation with the proliferation index Ki-67.

Methods: Our material comprised of 56 lymph-node biopsies from patients with nodular sclerosis (n=19) and mixed cellularity (n=37). The APAAP immunohistochemical method was performed on paraffin sections for the detection of p53, Rb, Waf1, Ki-67 (MIB-1) proteins with monoclonal antibodies. In parallel, the expression of Epstein-Barr virus (EBV) was investigated using the RASH and the APAAP methods for the detection of EBV.

Results: p53 protein was detected in 30% of the cases showing an heterogeneous nuclear expression in a limited number of neoplastic cells (5-10%). Rb and Waf1 proteins were detected in all cases. Rb protein was expressed in a high percentage of neoplastic cells (>25%) in the majority of the cases, while Waf1 demonstrated a variable expression. Ki-67 (MIB-1) was detected in all cases showing an heterogeneous expression in a limited number of R-s cells (<25%). In 34 cases, an inverse correlation between Rb/Ki-67 expression was observed with a parallel Rb/Waf1 expression in 20/34 of them. The expression of p53, Rb, Waf1 proteins was not correlated with EBV detection.

Conclusions: Rb detection in a high percentage of R-s cells in combination with decreased Ki-67 expression suggests that cell-cycle dysregulation may be involved in the pathogenesis of H.D.

MAST CELLS IN HODGKIN’S DISEASE EXPRESS CD 30 LIGAND AND ACTIVATE A HODGKIN DERIVED CELL LINE THROUGH CD30 LIGAND-CD30 INTERACTION

Daniel Molin1,2, Christa Sundström2, Uktra Larsson2, Zou Xiang2, Gunnar Nilsson2, and Gunilla Enblad1
1) Department of Oncology, Radiology, and Clinical Immunology, Genetics and Pathology, University of Uppsala, Uppsala University Hospital, Uppsala, Sweden.
2) Identification of Hodgkin’s disease (HD) is characterized by relatively few tumour cells, Hodgkin and Reed-Sternberg cells (HRS), surrounded by a large amount of bystander cells, e.g., mast cells. Our knowledge about the role of mast cells in HD is very limited. CD30 ligand (CD30L-CD15) a, T lymphocyte membro glycoprotein belonging to the tumour necrosis factor (TNF) superfamily, has been shown to be expressed by a number of the surrounding cells, e.g., eosinophils, and has been demonstrated to stimulate the proliferation of HRS in vitro.

Methods: We have studied 46 patients with HD (mean age 37 years, male/female ratio 1:3.1), diagnosed and treated at the Uppsala university hospital, between 1992 and 1996. Tumours were immunocytochemically analysed regarding the presence of mast cells in the tumours, mast cell expression of CD30L, and serum levels of tryptase (a mast cell specific protease). Human and murine mast cell lines, human cord blood cultured mast cells, and a Hodgkin derived cell line were studied by RT-PCR, flow cytometry, immunocytochemistry, and in a co-culture system for their expression of CD30/CD30L.

Results: When the tumours were double-stained with antibodies against tryptase and CD30L, cells morphologically resembling mast cells expressing both antigens were identified. There is a tendency of an association between nodular sclerosis histology and abundant mast cell (p=0.2), CD30L stained (p=0.3), and double-stained cell infiltration (p=0.7), and between bulky disease and abundant double-stained cell infiltration (p=0.08). No correlation was seen between mast cell infiltration and tryptase levels in serum (p=0.95). The expression of CD30L in the cell lines was found to transduce proliferative signals in a CD30+ Hodgkin derived cell line.

Conclusions: We have identified CD30L- mast cells in Hodgkin’s disease. CD30L-CD30 interaction in the cell line which mast cells can activate neighbouring HRS through direct cell-to-cell contact.

CD40L IS OVEREXPRESSED ON B CELLS IN HODGKIN’S DISEASE (HD): RATIONALE FOR A Pilot TRIAL USING ANTI-CD40 ANTIBODY

K. Caid, Z. Asary, S. Zhao, M. Younes, D. Wimmer, F. Cahanus, M. Anderson Cancer Center, and Baylor College of Medicine, Houston, TX; and St. Anna Children’s Hospital, Vienna, Austria.

Introduction: RS cells of HD express high levels of CD40 receptors, and exogenous soluble CD40L has been reported to enhance the survival of HD cell lines in vitro. We have recently reported that CD40L can rescue maliagnant B cells from spontaneous, PaL-induced and chemo-induced cell death. CD40L expressed on T cells of HD has been shown to influence lymph nodes or peripheral blood. Surprisingly, B cells of HD expressed high levels of CD40L. The mean % of HD peripheral blood B cells that expressed CD40L was 55% and on lymph node B cells 63%. In comparison, the mean % of B cells of healthy individuals that expressed CD40L was 9.9%. Both IL-4 and IL-10 significantly increased CD40L surface protein on B cells of normal individuals within 48 hours, whereas TGF-β had no effect. Neither one of these cytokines had an effect on CD40L expression in T cells.

Methodology: Normal B cells of HD over-express CD40L which can provide RS cells with survival signals. To test this hypothesis, we are studying the potential therapeutic role of anti-CD20 to eliminate normal B cells in patients with relapsed HD.
HODGKIN’S DISEASE CLINICAL STAGES II-I: A CLINICOPathOLOGICAL STUDY OF 281 PATIENTS

D. Coria M. Vasilescu, M. Gociu, D. Colota
Dept. of Haematology, Fundeni Hospital, Bucharest, Romania

In Hodgkin’s disease (HD) today is possible to accomplish high rates of cure after treatment. We undertook the present study to determine the bad prognostic factors in early stages HD. We reviewed retrospectively 281 patients (pts) with HD, diagnosed and treated in Fundeni Hospital between 1976-1996. Median age was 34.7 years (15-81 yrs); 150 pts were females (53.4%) and 131 pts (46.6%) were males. By stages 43 (15.3%) were in stage I and 238 pts (84.7%) were in stage II. B-symptoms were observed in 157 pts (55.9%). Histologic studies showed mixed cellularity (MC) in 113 pts (40.2%), nodular sclerosis (NS) in 85 pts (29.2%), lymphocytic predominance (LP) in 45 (16.1%), lymphocyte depletion in 25 pts (8.9%) and unclassifiable in 13 pts (4.6%). The following parameters were investigated for their prognostic significance: age (<45 yr), sex, clinical stage, B-symptoms, histologic subtype, number of involved nodal sites (<3), bulky mediastinal disease, ESRR (<50), HB (<14 g/dL), WBC (cros<10 x10^9/L), lymphocyte (cros<1500), Eos (cros<700), serum albumin (<30 g/dL), fibrinogen, α2-globulin. Initial treatment included only chemotherapy (CT) in 84 (29.8%), while the vast majority of pts 197 (70.1%) received combined modality therapy (CT+RT).

Complete remission was achieved in 233/281 pts (82.9%); no response to initial treatment in 48 pts (17%). Ten years survival rate was 82.5%. Causes of death were: HD progression (61%), infections (13%), second malignancy (11%) and heart disease (6%). Univariate analysis of prognostic factors revealed that age >45 yrs, B-symptoms, stage IIb, HB<11 g/dL, L<10.000/mL, Ly<1500/mL, ESRR<50 mmHg, Fg<400 mg/dL, Ab<3g/L had adverse prognostic significance. Conclusion: the analysis and characterization of bad prognostic factors could be helpful when designing special treatment strategies for these patients.

7. Hodgkin’s Disease
PRELIMINARY RESULTS OF VEPMB REMIG IN ELDERLY HODGKIN'S DISEASE PATIENTS.

Background and aim of the work. Advanced age is a negative prognostic factor for Hodgkin's disease (HD). However HD is uncommon in later life and there are only few data on elderly HD patients (pts). The preliminary results of a new regimen (VEPMB) devised for elderly pts are presented.

Patients. Between 1996 and 1998, 53 HD pts older than 65 years were prospectively treated with the VEPMB regimen: vincristine 6 mg/m² i.v. on day 1, cyclophosphamide 500 mg/m² i.v. on day 1, procarbazine 100 mg/m² i.v. per day 1 through 5, prednisone 30 mg/m² i.v. per day 1 through 5, etoposide 60 mg/m² p.o. days 15 through 19, mitoxantrone 6 mg/m² i.v. on day 15, bleomycin 10 mg/m² on day 15. The regimen was scheduled every 28 days. Stage IIA and IIA pts received 3 courses of VEPMB followed by involved field irradiation. Patients with more advanced disease underwent 6 courses of VEPMB and radiotherapy limited to the areas of bulky disease.

Results. Mean age was 71 years (range 65-80). Age related comorbidity was present in 20 pts (38%). 27 pts were in stage I and IIA and 26 in more advanced stage (55% in stage IV). No toxic deaths were observed. No treatment interruption for toxicity or poor patient compliance was observed in stage I and IIA pts and all of them completed their 3 courses. In more advanced stage the treatment was interrupted in 4 pts: 1 for disease progression, 2 for poor compliance, and 1 for death due to unrelated cause. All pts treated with 6 courses experienced at least one episode of grade 3-4 neutropenia. However hospitalisation for fever was necessary in only 3 cases. 37 pts are so far evaluable for final response: CR was obtained in 100% of stage I and IIA patients and no response was evident so far. In more advanced stages the results were: CR 44%, FR 28%, NR 28%.

Conclusions. The VEPMB regimen is feasible in elderly HD. Preliminary results are good in I and IIA pts. In more advanced stages results are less favourable, but a higher number of pts with a longer follow up is needed in order to compare it with alternative strategies.

7. Hodgkin's Disease

CARCINOMA FUNCTION ASSESSMENT AFTER TREATMENT OF HODGKIN'S DISEASE.
O. Nasibov, S. Pasha, A. Pivnik, V. Sotnikov*, N. Razeghiv Research Centre for Haematology, Research Centre for Diagnostic and Surgery*, Moscow, Russia.

Purpose. The treatment of Hodgkin's disease (HD) involves radiotherapy and chemotherapy. Both modalities may cause heart injury.

Methods and Materials. We examined by equilibrium radionuclide angiocardiography (ERA) the cardiac function of 41 patients (1 male, 30 females) who received chemotherapy (6-12 courses COPP/CHOP and/or MOPP) and mediastinal radiotherapy in different doses (35-50 Gy) from 1973 to 1995. The median patients age was 45.1 (range 33-66 years) at the time of the evaluation. Eighteen healthy individuals (11 males, 7 females) were examined as controls. ERA was used to elucidate the left ventricular systolic and diastolic function by measuring left ventricular ejection fraction (LVEF) and peak filling rate (PFR).

Results. Patients in the main group had a lower mean left ventricular ejection fraction than those in the control group, 55.5±1.5% (normal > or =50%) versus 63.4±2% (P<0.05). Patients in the main group had a lower mean PFR. 2.03±0.078 end diastolic volumes per second (EDV/s) than those in the control group 2.31±0.088 EDV/s (P<0.05).

Conclusion. The mean LVEF and PFR in the main group were normal. ERA screening after curative treatment in patients with HD showed minimal changes in cardiac function.

TOXICITY AND FEASIBILITY OF THE BEACOPP REGIMEN FOR ADVANCED STAGE HODGKIN'S DISEASE PATIENTS OLDER THAN 65 YEARS.

Introduction. The chemotherapy regimen BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) has been shown to be feasible and effective for patients (pts) up to 65 years old in the GHS HDG randomized trial. The present report aims to assess the applicability of this regimen for older pts.

Methods. From 3/93 until 10/97, 64 pts. between 66 and 75 years were assigned (until 6/96: randomised) to standard alternating COPP/ABVD (arm A, n=26) or to BEACOPP baseline dose (arm B, n=38) therapy. Eight chemotherapy cycles were planned, followed by irradiation of any initial bulky and residual disease. The two regimens were approximately equivalent in dose, but the BEACOPP cycle was 7 days (25%) shorter.

Results. 62/64 Pts. were evaluable. Hamaotological toxicities under BEACOPP were more severe for these older pts than for younger pts, with 88% WHO grade 4 leukopenia and 48% grade 3 or 4 thrombocytopenia. Under COPP/ABVD these toxicities were less frequent: 38% and 15% respectively. Other toxicities were not increased. 8/36 pts. terminated BEACOPP early due to toxicity and 3 for other/unknown reasons. Only 19/36 pts. received all 8 BEACOPP cycles. The given dose of all BEACOPP drugs (except prednisone) was considerably reduced: between 34% (doxorubicin) and 73% (vincristine) of pts. received less than 80% of planned dose. Reduction was more pronounced than for COPP/ABVD. G-CSF was given in 37% of BEACOPP cycles. The median duration of complete BEACOPP administration was 26 weeks (protocol: 23 weeks), compared with 36 weeks for COPP/ABVD (protocol: 30 weeks). With a median observation time of 33 months, 14 BEACOPP and 10 COPP/ABVD pts died, 7 and 1 pts. respectively of acute toxicity and 4 and 6 pts. respectively of their disease. Survival and freedom from treatment failure rates at 30 months (arms nearly identical) were estimated as 57% and 53% respectively (95% confidence limits: 43-72% and 39-67%). These should be compared with the 92% and 79% rates, respectively, for younger pts. with baseline BEACOPP.

Conclusions: These preliminary results suggest that BEACOPP (baseline dose) shows considerable acute toxicity in older pts, requiring frequent dose reduction. This scheme should be modified for older pts., perhaps with regular administration of G-CSF. Escalated BEACOPP would not seem to be an option for pts. over 65.
PHASE II STUDY OF A 14 DAY VARIANT OF THE BEACOPP REGIMEN IN PATIENTS WITH ADVANCED STAGE HODGKIN’S DISEASE


Introduction: Improvement of treatment results in advanced stage Hodgkin’s disease has been achieved by dose escalation of the BEACOPP regimen in a 14-day cycle (B21). An alternative approach to intensify therapy is to shorten cycle duration. With the aim of improving toxicity profile while maintaining treatment results, the GHSIG started a phase II study to examine the possibility of reducing the BEACOPP baseline dose scheme in a 14-day cycle (B14). Primary aim is to assess the feasibility of B14 in a respect of complete and punctual administration. The secondary objective is the characterisation of side effects, in particular hematotoxicities.

Methods: Since September 1997, 27 centres recruited 86 patients with Hodgkin’s disease stage IIB, III and IV. The regimen consisted of 8 cycles B14 with obligatory application of G-CSF, followed by radiotherapy to initial bulky and residual disease. A first interim analysis in 1999 included all 53 patients with full documentation of the given chemotherapy.

Results: The analysis demonstrated a median chemotherapy cycle duration of 15 days (range 13 - 27). 83% of patients completed their cycles in under 21 days. For each dose, a reduction of more than 20% was made in less than 20% of the patients, which is comparable to the results of the B21 baseline. WHO grade III and IV toxicities per patient were as follows in comparison with BEACOPP baseline and escalated:

<table>
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<tr>
<th>WHO grade III/IV</th>
<th>B14 (24 weeks)</th>
<th>B21 Baseline (24 weeks)</th>
<th>B21 escalated (24 weeks)</th>
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<tr>
<td>Leukopenia</td>
<td>87%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Thrombocytopenia</td>
<td>78%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13%</td>
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Conclusion: The BEACOPP 14 regimen can be applied without undue delay. Dose reduction was not more frequent than for baseline B21. Toxicities were less than for escalated B21. This accelerated BEACOPP variant seems to be feasible. Since final treatment results are currently pending by ongoing radiotherapy, the evaluation of response rates will be presented in June.

EOSINOPHIL INFILTRATION IN LYMPH NODES IS AN INDEPENDENT PROGNOSTIC FACTOR IN HODGKIN’S DISEASE

J. Franklin, R. von Wasielewski, U. R. Sieh, A. Georgii, and V. Diehl
Universitäts Klinik, Cologne and Medizinische Hochschule, Hanover, Germany

Introduction: Histological subtype has been shown to have a modest but significant prognostic relevance in Hodgkin’s disease (HD), especially for nodular sclerosis grades I and II (NSG, NS2). We aimed to identify those morphological characteristics most strongly correlated with prognosis and to investigate this correlation. This report focuses on the role of the lymph node eosinophil density.

Methods: Several morphological characteristics (morphometric, infiltration pattern, surrounding lymphocytes, sclerosis, capsule, cellular composition, tumour cell morphology, granulocytes, eosinophils) were examined and classified for all available slides of lymphoma tissue from HD patients (n=1). In 1985, 91% of the studied HD cases were treated in one of the three groups according to stage and risk factors: early stage pts. received extended field radiotherapy (40-60 Gy), intermediate stages two double cycles of COPP/ABVD chemotherapy followed by extended field and advanced stages four double cycles COPP/ABVD followed by local irradiation. The characteristics were tested for correlation with freedom from treatment-related (FTT) and survival (S) univariately using the Kaplan-Meier method, and multivariately using Cox regression analysis allowing for the factors age, Karnofsky performance status, stage, B symptoms, histological subtype, large mediastinal mass, E-stage and stage in the international prognostic index for advanced HD. All analyses were stratified according to treatment group.

Results: Among the morphological factors, eosinophil density was the only one consistently and highly significantly correlated with treatment results. In the 1985 investigated cases, the 150 cases (28%) with tissue eosinophilia had a 5% lower FTTP and a 7% lower SV than the remainder (both p<0.001). This effect was observed separately in all 3 treatment groups and in NS1, NS2 and NC histological subtypes. In multivariate analyses, eosinophil count was an independent prognostic factor for poorer outcome in FTT and survival. Conclusions: High eosinophil density is an independent predictor of poorer outcome in Hodgkin’s disease. Further investigation of the biological and clinical relevance of this factor is required, in particular its relationship to other histopathological factors such as the markers CD51 and ILS.

REDUCED DELIVERY OF CHEMOTHERAPY TO ELDERLY PATIENTS WITH HODGKIN’S DISEASE: A CONTRIBUTOR TO POOR OUTCOME?

N. Callafetis, M. Crump, B. Zanke, M. Gospodarowicz
The Princess Margaret Hospital and Toronto General Hospital, Toronto, Ontario, Canada

Introduction/Methods: Hodgkin’s Disease (HD) in patients (pts) age ≥60 years is associated with inferior cause-specific survival (CSS). To assess the role of reduced treatment intensity in this inferior outcome, we evaluated the delivery of radiation (RT) and chemotherapy (CT) to 136 consecutive pts ≥60 treated at 1980-1995, and compared this to a random cohort of pts age ≥60 (n=70) matched by CT regimen. Total dose (TD, mg/m²) and dose intensity (DI, mg/m²/week) of each drug in a multidrug CT regimen were expressed as a percentage of that intended by the treating physician. Results: Most elderly pts had nodular sclerosis (NS, n=50) or mixed cellularity (MC, n=50) histology. Most pts ≥60 had NS HD (n=53), while MC (n=12) and LP (n=2) HD were less common. B symptoms were present in 38% of elderly and 93% of younger pts. 99% of pts ≥60 were planned to 90% of elderly pts and in 96% of younger pts. For those who received CT (n=76, age ≥60 and n=87, age <60), dose reductions occurred in 58% and 47%, while treatment delays occurred in 53% and 14% respectively. Elderly pts treated with MOPP (n=25) received mean 57% of planned TD, while younger pts (n=50) received mean 80% (p=0.009). The mean relative DI for the elderly group was 69% and for pts ≥60 was 82% (p=0.03). Older pts treated with ABVD (n=17) received mean TD 65%, while younger pts (n=54) received mean TD 92% (p=0.0002). The mean relative DI was 68% in the older group, and 82% in pts ≥60 (p=0.041). None of the elderly pts received G-CSF during ABVD, while 6/10 pts ≥60 did. CT reductions/delays in those ≥60 were most often due to prolonged myelosuppression, toxicity or infection, while myelosuppression was the main reason in pts <60. CT discontinuation was due to toxicity and pt refusal in pts ≥60, but disease progression in the younger group. Overall CR rate was 84% in those ≥60 years and 91% in those <60 years. CSS at 5 years for all pts who received CT was 85% in the elderly, 91% in the elderly, 91% in the elderly, 97% in the younger group (p=0.0001), log rank test). In multivariate analysis (Cox), TD ≥70%, age ≥45 and hemoglobin <10.5/g/dL were found to be independent predictors of CSS, while DI ≥70%, histology, male sex, and stage IV disease were not. Discussion: One of the factors that suggests different outcomes exist between elderly and young pts with HD, and that elderly patients have more prognostic factors. It also suggests that reduced systemic toxicity (TD or DI), as has been shown to occur in elderly pts with lymphoma, may be an important factor contributing to the inferior CSS seen in elderly pts with HD.

7. Hodgkin’s Disease
MONOCLONAL GAMMOPATHIES IN PATIENTS WITH HODGKIN'S DISEASE

G. Milicević, R. Janičić-Mededjik, B. Mihaljević, S. Janković, V. Čemerezić, Petrović
1 Institute of Hematology, 2 Department of Pathology, Clinical Center of Serbia,
Belgrade, Yugoslavia

INTRODUCTION: Serum monoclonal immunoglobulins (Iggs) bands have been described in a variety of disease states as well as asymptomatic individuals and "well" elderly, but are most consistently associated with lymphoid malignancies. Lymphoma, especially B cell lymphoma represents a single immunoclonal cell, and as such it is paradigm of monoclonality. Since Iggs are synthesized by cells of the B lymphocyte lineage it is possible that in some cases these M components are produced by lymphoma cells.

METHODS: In this study we examined 46 patients (pts) aged from 19 to 59 years in period of 24 months. All of them had histological confirmation of Hodgkin disease (HD) according to criteria defined by REAL classification. Practically all pts received chemotherapy, radiotherapy or a combination of both. However hematologic and immunologic data were almost always obtained prior to therapy. Serum samples were tested immediately or stored at -20°C until use. Twenty four hour urine collections were obtained. Routine electrophoresis of serum proteins was performed in all cases with "Chemotron" cellulose electrophoresis apparatus. Monoclonal peaks were typed by immunoelectrophoresis by agar gel technique. Antibodies against various Iggs and light chains were obtained from "Behringwerke". The specificity of these antisera was checked in laboratory against known standards. Additional studies included concentration of total protein, gamma globulins and electrophoresis of urine concentrate for Bence-Jones protein. We used IBM computer 386 with "Statistical Package for Social Science" v.3.8 for statistical data.

RESULTS: There were 30 men (65,2%) and 16 women (34,8%). The most frequent clinical stage was II (56,5%). There were 13 patients (28,2%) with nodular sclerosis with mixed cellularity. We found out in sera and urine of our pts one pt with nodular lymphocyte predominant HD (NLPHD) and IgG kappa M protein. The serum concentration of total protein in pt with M component in several samples ranged from 70,4 g/l to 81,8 g/l (median 78,13 g/l) and in others median was 68,16 g/l. We used t-test and this difference was significant (p<0.05).

CONCLUSIONS: In NLPHD a unique B cell phenotype is common (almost 100%) but is uncommon in other subtypes. Mixed cellularity or nodular sclerosis with NLPHD is highly analogous to follicular small cell lymphoma, also of germinal center origin. The association of M components with lymphoproliferative disease is well established. Our own series of 46 pts with HD had 1 pt with M component.

7. Hodgkin's Disease

SECOND MALIGNANCIES AFTER THERAPY FOR HODGKIN'S DISEASE

L. Cheveresan, H. Ionita, L. Roht, M. Cheveresan
Hematology Department, University of Medicine and Pharmacy - Timisoara, Romania

INTRODUCTION. Patients cured from Hodgkin's disease (HD), develop second malignancies with a higher incidence than expected in the general population. Both chemotherapy (CT) and radiotherapy (RT), alone or combined, may contribute to the risk. Purpose of this study is to determine risk factors and types of second malignancies, as well as the incidence in long term survivors from HD.

METHODS: Between 1980-1996, 715 adult patients were treated for HD at the City Hospital Timisoara. Therapy consisted of CT alone - 45,7%, RT alone - 3,9%, combined modality (CT+RT) - 44,6%, and CT+RT plus pelvic chemoradiotherapy - 3,7%. All stages and histopathologic subtypes were represented. For each group of initial therapy incidence of second malignancies was assessed, and a comparison with the general population was also made. RESULTS: 715 patients, 382 malignancies were observed at some time after achieving complete remission; in one case chronic lymphocytic leukemia developed during the evolution of HD. Malignancies encountered were: 2 breast cancers, 1 lung cancer, 1 urothelial cancer, 1 non-Hodgkin's lymphoma, 2 acute myeloblastic leukemias. Median time interval for occurrence of second malignancies was 68 months. Median observation time was 7.2 years. CONCLUSIONS. Second malignancies are an important late effect of HD therapy. In our study the risk for second malignancies was strongly associated with the combination CT+RT+pelvic radiation therapy compared with the combination CT+RT radiation therapy and for hematological malignancies, and with RT (irradiated fields) for solid tumors.

FOLLOW-UP OF HODGKIN'S DISEASE TREATED PATIENTS WITH THYMIC REACTIVE HYPERPLASIA.

Hematology-Lymphoma Clinic «Evangelismos» General Hospital, Radiologic Department «Evangelismos» General Hospital, 2nd Radiotherapy Department** «St. Savvas» Anticancer Hospital, Athens, Greece.

Introduction: The occurrence of benign thymic hyperplasia is recognized in a small proportion of patients, particularly in children, following administration of chemotherapy for lymphoma diseases and solid tumors. However, it has rarely been reported in Hodgkin's disease adults patients. The purpose of our study was to describe this phenomenon, since it is important to distinguish it from residual or recurrent Hodgkin's disease.

Method: We reported 7 cases of thymic hyperplasia of 109 patients (6%), who were treated successfully with standard combination CT (ABVD or hybrid MOPP/ABV) between 1990-1998. The median age of those 7 patients was 27 years of age (range 18-43 years of age).

Results: In all patients, diffuse thymic enlargement was noted in a period of 6 months, after the completion of chemotherapy, and while patients were in full clinical remission. For the evaluation of thymic hyperplasia, the patients were followed by chest x-rays, chest CT-scan, gallium-67 scans. Tissue diagnosis was performed in only 1 patient. The addition of mantle RT in 2 of 7 patients, according to the treatment plan, did not affect the thymic enlargement. All patients remain in complete remission and the thymus dimensions gradually self-decreased, with a median follow-up time of 45 months (range 11-65 months).

Conclusions: The appearance of an anterior mediastinal mass after successful treatment of Hodgkin's disease, should not be mistaken as a recurrence of the disease. It may be due to rebound thymic hyperplasia, particularly when the mediastinum has not been previously involved and there is no clinical or radiological evidence of recurrent disease elsewhere.
Pathological and clinical characteristics of 76 Hodgkin's disease (HD) patients misclassified in a lymphoma protocol (LNHST7)

Hôpital Dieu, Paris, France

The REAL classification defines clear criteria to distinguish NHL and HD and identifies a provisional entity placed on the borders between the two diseases, the so-called large-cell lymphoma/Hodgkin-like (ALCL-HL). However, the reality of the ALCL-HL entity is now debated. Between 1987 and 1993, 76 out of 2855 lymphomas included in the LNHST7 protocol as NHL or ALCL-HL, had diagnostic recidive to HD after revision and complete immunohistochemistry (applied on paraffin-embedded sections with CD30, CD15, CD20, CD3, CD45, CD43, TACT1, BCL2, LMP, EMA, ALK1 antibodies). The purpose of our study was to analyze the various pathological parameters encountered, and to follow the survival of these 76 patients affected with HD and treated initially with NHL protocols.

Among the 76 lymphomas, 12 were easily recognized as HD after one revision (Group A). The diagnoses of the 17 ALCL-HL (Group B) and the 13 T-cell NHL (Group C: AILD 5, lymphophasic: 4, others types: 4) were rectified to HD after a second revision and complete immunohistochemistry. None was ALK1 positive. These 76 HD were classified according to Lukes classification and INHL grading as follows:

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The main clinical characteristics were: median age: 37 (range: 16-83), stage I: 78%, II: 49%, III: 9%, and IV: 35%, B symptoms: 52% and bulky mediastinum: 21%. According to EORTC index for stage I and II, 35% were favorable and 65% unfavorable. For advanced stages, the International Prognostic Score was ≤2: 21%, 3: 30%, 4: 49% and ≥5: 9%. Fifty-five percent of the patients completed the full HD treatment according to the LNHST7 protocol. The 5-years DFS was 53% and the 5-years OS was 76%.

Mains pitfalls focused on difficulties to differentiate HD (type 1, 2, and 3) from T-cell NHL, on one hand, and HD (type 2 and grade 2) from ALCL-HL on the other hand. ALCL-HL subtype was overdiagnosed, because of unclear and subjective criteria.

VALIDATION OF THE PROGNOSTIC SCORE DERIVED FROM THE INTERNATIONAL PROGNOSTIC FACTORS PROJECT (IPPF) FOR ADVANCED HODGKIN'S DISEASE IN PATIENTS FROM A SINGLE HEMATOLOGY UNIT.

1. Dept of Pathology, National Centre of Haematology and Transfusionology, Athens, Greece.
2. Dept of Pathology, National Centre of Haematology and Transfusionology, Athens, Greece.
3. Dept of Pathology, Univ. Hospital of Heraklion, Crete, Greece.

INTRODUCTION: Recent studies suggest that cell cycle molecules regulating G1-S phase transition play an important role in oncogenesis, but little is known about their involvement in Hodgkin's Disease (HD). The aim of this study was to investigate the immunohistochemical distribution patterns of p16 and pRb in HD and compared to MDM2 protein status and the presence of Epstein-Barr Virus (EBV) in HD.

METHODS: In 44 HD cases we applied sensitive immunohistochemical methods using monoclonal antibodies to analyze the expression of all four proteins. Our findings were correlated with the presence of EBV examined by RNA in situ hybridization (RISH) and clinicopathological parameters.

RESULTS: p16INK4A protein immunoreactivity was found in all 44 cases with a variable proportion of Hodgkin-Reed-Sternberg (HRS) cells ranging from 30% to 90%. In 93% of the cases studied, pRb was detected in HRS while all cases showed overexpression of p53. Almost all specimens (98%) were MDM2-positive as evaluated by IHC and/or ifp2 monoclonal antibodies. EBER 1/2-transcripts were detected in 31.8% (7/44) of the examined samples. A significant correlation immunoreactivity of p16INK4A and MDM2 and the number of HRS cells was observed (p=0.0012 and p=0.0018, respectively). In a subgroup of cases with more than 50% of HRS cells positivity, p16INK4A protein levels were inversely related to those of p16. All clinicopathological parameters and clinical prognostic indicators including duration of response to therapy were not statistically related to the expression levels of all four investigated proteins and the presence of EBV.

CONCLUSIONS: Our findings suggest that p16 and pRb are regularly expressed and their pathway in cell cycle machinery seems to be intact in HD. However, further investigation is needed in order to shed light on cell cycle molecules' involvement in Hodgkin's lymphomagenesis and follow up of the patients is required for conclusive clinical implications.
TREATMENT OF EARLY STAGE HODGKIN'S DISEASE (HD) WITH CHEMOTHERAPY (CT) ALONE USING A NON-ALKYLATED REGIMEN EBVP/MV: A PROSPECTIVE SINGLE CENTER STUDY.

Service d'Hématologie Clinique, Hôpital-Dieu, 75181 Paris cedex 04, France.

Introduction: Long term survival of patients with HD is hampered by treatment-related complications. Whereas further significant improvement of HD control is unlikely in early stages, the aims of current strategies should be the reduction of these complications by reducing or suppressing radiation therapy (RT) and/or avoiding the use of alkylating agents.

Methods: 1. We designed and evaluated the efficacy and tolerance of EBVP/PV regimens as initial treatment of HD. Each course of Eribulin 35 mg/m² D1 & D15, Bleomycin 10 mg/m² D1, Vinblastine 6 mg/m² D1 & D15, Prednisone 80 mg/m² po D1 to D5, Methotrexate 35 mg/m² D1 and Etoposide 80 mg/m² iv D15 and 150-200 mg po D16-D17 were repeated at a 4-week interval. 2. Patients (pts) with early stages (I and II) and without unfavorable prognostic factors (EORTC criteria) were planned to receive CT alone, providing they had achieved CR after 4 courses. Otherwise, they received Involved field RT (36-40 Gy).

Results: From 1993 to 1998, 42 pts were treated: M 26/F 16; median age 30 yrs (16-58); CS I 10, CS II 24, CS III 4 and CS IV 4. All pts received 4 to 8 courses, according to stage, prognostic factors and status after 4 courses. Thirty-three of 240 courses (13%) have been postponed mainly because of neutropenia, but infection grade 3 or 4 was not observed. After 4 courses, 74% pts were in CR and 26% in PR. Among the 34 pts with early stages, 27 have completed treatment and all achieved CR. Three of the 13 pts who did not receive RT (median FU 34 mo, range 7-55) had relapsed in initially involved sites at 6, 7 and 25 months (estimated 3-yrs EFS 67 ± 15%), whereas there was no relapse so far in those who received RT (n = 14, median FU 16 mo). One patient died at 57 mo from secondary bronchic carcinoma.

Conclusions: EBVP/MV is feasible and gives expected results in early stage HD. RT is likely not mandatory in all cases of localized HD but the relapses we observed after CT alone justify the evaluation of this strategy within controlled cooperative trials.

TREATMENT OF EARLY-STAGE HODGKIN'S DISEASE WITH FOUR CYCLES OF ABVD FOLLOWED BY LIMITED RADIOTHERAPY: ANALYSIS OF EFFICACY AND LONG-TERM TOXICITY

E. Brusamolino1, A. Baggio1, P. Luriti1, E. Orlandi1, C. Astori1, C. Baralet1, G. Pagnucco1, G. Castelli1, M. Lazzaroni1, F. Franchini1, C. Bernasconi1. Istituto di Ematologia, Universita di Pavia1, Servizio di Radioterapia Clinica2, RCCS Policlinico S. Matteo, 27100 Pavia, Italy.

Introduction: The use of combined modality therapy in early-stage Hodgkin's disease can spare staging laparotomy, allows smaller field and lower dose of radiation and reduces the risk of relapse compared to radiation alone. This paper reports on the results and long-term events of a combined modality approach consisting of a brief chemotheraphy (CT) and limited radiotherapy (RT) without staging laparotomy in patients with early-stage Hodgkin's disease.

Methods: This prospective study included 98 patients (20 with clinical stage I and 58 with stage II), 60% of total had mediastinal enlargement, 12% bulky disease, 6% B symptoms and 5% subdiaphragmatic disease. Median age was 33 years (range: 15-64) and median follow-up 56 months. The treatment program consisted of 4 cycles of the ABVD regimen, as originally described, followed by limited RT on involved sites (44 patients) or involved and contiguous sites of disease (54 patients). Radiation dose ranged from 30 to 36 Gy to uninvolved and involved sites, respectively, bulky disease received up to 44 Gy. Gonadal function in women was assessed by hormonal tests and menses evaluation; fertile women were given an estrogen-progesterone combination for ovarian protection, while most of young men had their semen cryopreserved.

Results: The treatment program was completed in a median of 6.2 months (range: 5-10). Complete remission (CR) rate was 88% after 4 ABVD (69 patients) and 58% after the adjunctive RT. The 5-year relapse-free survival (RFS) is 97%, two of 3 relapsing patients had achieved only partial remission after ABVD. The 5-year overall survival is 98%; two patients died to date, one of disease progression and one of small cell lung carcinoma. Therapy-related long-term toxic events included two cases of pulmonary fibrosis with symptomatic interstitial disease, one case of dilated cardiomyopathy with cardiac failure (all patients had received mediastinal irradiation), and hypothyroidism requiring replacement therapy in five cases. Fertility was preserved in young women and four normal pregnancies were registered. No cases of secondary leukemia occurred.

Conclusions: In early-stage Hodgkin's disease not undergoing staging laparotomy, the combination of a brief CT consisting of 4 cycles of ABVD and limited irradiation was effective and produced a 97% RFS at 5 years. A prolonged monitoring of potential long-term sequelae of therapy and evaluation of their impact on the quality of life are mandatory in this curable setting of patients.

TREATMENT OF ADVANCED HODGKIN DISEASE (HD): LONG-TERM RESULTS OF ALTERNATING CHEMOTHERAPY PROGRAM (MOPP/BCAVI).


With the purpose to determine efficacy and security of an alternating seven-drug chemotherapy program, we used MOPP/BCAVI for untreated advanced (Ann Arbor Stage III-IV) HD. From april'83 to march'93, 63 consecutive pts were included in this study. Staging was done according with Ann Arbor criteria and costs and did not reach 100% of the cases. RESULTS: Forty-six men and 17 women, median age 28 and 38 yo, respectively. 14 were in stage III-A (22%), 32 III-B (51%) and 17 IVB (27%). Performance Status (PS, ECOG) 0-1 in 46 (73%) and 2-3 in 17 (27%); 77% of pts had B symptoms. More frequent history was mixed cellularity (52%), followed by nodular sclerosis with 27%. Overall response was 91% (CR 72%, PR 14% and progressive disease in 5%). On univariate analysis, only PS was statistically significant to obtain CR. For a 180 months of maximum follow-up, there was an overall survival of 83%. For CR pts, OS and DFS was 97%. The last relapse was seen at 16 months. PS and number of courses for achieving CR were significantly related to OS and DFS. PS 0-1 vs 2-3 had an OS of 90 and 63% respectively (p=0.0087), the OS for pts who achieved CR with 1-3 and 4-6 courses was 97 vs 72% respectively (p=0.00007). Haematologic toxicity grade 3-4 was seen in 7% of courses. Toxicity-related death occurred in 7 pts (12%). CONCLUSION: This results suggest that MOPP/BCAVI is a highly active chemotherapy program. Nevertheless, their toxicity could be ameliorated with better supportive measures. PS seems to be a very important factor influencing response and survival.

7. Hodgkin's Disease