Lymphoma

Hodgkin's Disease

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HODGKIN DERIVED CELL LINES L540 AND L540cy GROW DISSEMINATEDLY IN SEVERE COMBINED IMMUNODEFICIENT (SCID) MICE

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An animal model with disseminated growth of Hodgkin cells would be useful for preclinical testing, since new immuno-therapeutic strategies will be employed in patients with disseminated disease. Therefore, the Hodgkin derived cell lines L540, L540cy, L428 and KM-H2 were injected intravenously into SCID mice. In contrast to L428 and KM-H2, widespread neoplasia occurred after a period of 4-6 weeks following injection of L540 and the subline L540cy. The lymph nodes were found to be the preferred site of tumor growth. The CD30 surface antigen on Hodgkin cells and the karyotype of the cells were preserved in the animal host. Thus, the SCID mouse model mimics to a large extent the dissemination pattern of Hodgkin's disease in man and may provide a useful tool for evaluation of the efficacy of conventional and newly developed therapies. To evaluate the role of adhesion molecule expression in the dissemination of Hodgkin-derived cell lines, CD44 and members of the immunoglobulin, integrin, selectin and Fc receptor families were quantified by flow cytometry. CD30 expression was also measured. Although CD44 expression has been correlated with dissemination in non-Hodgkin lymphoma, this was not the case in the Hodgkin SCID mouse model. CD44 was not expressed on the disseminating cell lines L540 and L540cy.

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RADIOTHERAPY ALONE VS RADIOTHERAPY PLUS CHEMOTHERAPY (ONE COURSE ABVD) IN STAGE II pA HODGKIN'S DISEASE WITH MEDIASTINAL LOCALIZATION.

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Between 1983 and 1992, 79 pts pathological stage IIA Hodgkin's disease with mediastinal localization were treated at the Depts. of Radiotherapy and Ematology of the University "La Sapienza" of Rome.
Patients were randomized before submission to therapy: a first group of 39 pts, received Radiotherapy alone (RT) with mantle and para-aortic lymph-nodes irradiation (sTNI) to a total dose of 44 Gy on the originally affected lymph-nodes, 40 Gy on mediastinum and 36 Gy on the clinically uninvolved limph-nodes.
The second group of 40 pts received one course of chemotherapy (ABVD) before undergoing radiotherapy with same modalities of the first group. The total follow-up of the first group varied between 11 and 113 months (median 71 months) after treatment and between 4 and 119 months (median 67 months) for the second group.
In the first group 37 pts (95%) obtained complete remission (CR) whereas 2 pts (5%) with disease progressed and, were administred salvage chemotherapy (6 alternate cycles of MOPP-ABVD) obtaining CR. All the 40 pts of the second group obtained CR. We observed 10 relapses (25%) in the first group versus 2 (5%) in the second one whereas the free of disease survival at five years was respectively of 73% and 95%; this difference, studied with log-rank test, resulted of statistical relevance ($P < 0.05$).
Incidence of complications in the two groups is similar; however pts undergoing RT plus ABVD presented a higher incidence of lung fibrosis than cases treated with RT alone. A patient of the second group developed non limphoid acute leukemia and died at 38 months of follow up.
This series confirms a better outcome without developing major complications for cases in early stage and negative prognostic factors treated with combined modalities treatment.

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FEASIBILITY OF AN INTENSIVE COMBINED APPROACH IN ADVANCED HODGKIN'S DISEASE (HD). V.Bonfante, A.Santoro, L.Devizzi, S.Viviani, M.Balzarotti, M. Zanini, F. Soncini, R. Zucali, P. Valagussa and G. Bonadonna. Istituto Nazionale Tumori, Milan, Italy.
In an attempt to increase the cure rate of advanced HD, in 1990 we developed the regimen VEBEP: VP16 120 mg/mq i.v. x 2 days, epirubicin 40 mg/mq i.v x 2 days, bleomycin 10 mg/mq i.v.on day 1, cyclophosfamide 500 mg/mq i.v. x 2 days and prednisone 50 mg i.m x 7 days. Therapy was recicled every 21 days. The program included 8 courses followed by involved field RT 30-36 Gy. From 9/90 to 1/93, 79 pts PS IIB-III-IV or relapsing from primary RT entered and 54 were evaluable with a median follow up of 19 months (range 9-28). Main characteristics were: M/F 28/26; median age 28 yr (16-58); PS II 23, PS III 12, PS IV 11; relapsed after prior RT 8; B symptoms 42; bulky disease 14; extranodal extent 22; > 3 involved sites 38. CR was 95% and PR 3.7%. Four pts relapsed with a median time of 3.5 months from the end of treatment. WHO toxicity included: alopecia in 100%, Grade 4 leukopenia in 38%, Grade 4 neutropenia 85%, with a median duration of 4 days. Grade 2 anemia in 23%. All pts received antibacterial and antifungal prophylaxis. Infectious episodes were documented in 6% of cycles, requiring an hospitalization in 2%. One toxic death due to sepsis occurred in a 58 yr old man with bone marrow ipoplasia after prior TNI. Full doses of the planned schedule were administered in 97% of cycles; only 13% of them have been delayed for leukopenia. VEBEP is feasible and well tolerated; the incidence of CR may be slightly superior to that achieved with MOPP/ABVD. A longer follow-up is required to fully evaluate the cost/benefit ratio including sterility and second malignancies.

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OUTCOME OF STAGE III HODGKIN'S DISEASE. A RETROSPECTIVE ANALYSIS AFTER A MEDIAN FOLLOW UP OF 13 YEARS

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We retrospectively reviewed all patients [pts] with Stage III Hodgkins Disease admitted for staging or treatment between 1970-79 to the University of Chicago. Out of 96 pts we excluded 2 pediatric cases, and 1 pt, where no data was available. The median follow-up was 12.9 years (1.5-22.6 yrs). There were 54 males and 39 females. The median age was 28 yrs (15-67). Staging laparatomy confirmed all stages but one. Substage III_1 consisted of 42 pts, and III_2 had 51 pts. Histology consisted of the following: nodular sclerosis 54 pts, mixed cellularity 29, lymphocyte predominant 6, and 4 pts were unclassifiable. 85 pts were evaluable for response. 76 (89%) achieved a CR. A total of 36 pts died. In 24 pts, cause of death was related to Hodgkins disease. Second malignancies were observed in 10 pts (4 lung, 1 sarcoma, 1 bladder, 2 Non-Hodgkins-Lymphoma, 1 AML, and 1 MDS). The 10 yr survival in this study was 77%$\pm$5% (median 17 yrs). Multivariate analysis for survival was only significant for substages 1 and 2 (A+B). Median survival was 18.2 and 12.0 yrs ($p=0.03$ Gehans-Wilcoxon). When compared by stage (III_1A vs III_2A, etc.) this difference was not significant. The spleen size and delay from first symptoms to therapy did not predict outcome. The disease free, but not overall survival was superior for nodular sclerosing histology (73%$\pm$7% at 10 yrs), compared to mixed cellularity (43%$\pm$10%; $p=0.02$).

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AUTOLOGOUS BONE MARROW TRANSPLANTATION AND RADIOTHERAPY IN PATIENTS WITH HODGKIN'S DISEASE

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High dose chemotherapy and autologous bone marrow transplantation (ABMT) is often considered the treatment of choice for patients with relapsed advanced Hodgkin's disease (HD). The additional role of radiotherapy (RT) is unclear. We reviewed 15 patients irradiated 1-15 months after ABMT to assess the toxicity of RT. All patients had residual or relapsed HD at the time of irradiation. Grade 3-4 haematological toxicity occurred in 8/9 patients with initial stage III-IV disease, including all 5 given extended fields, but in no patient with stage II disease at presentation ($\chi^2=10.39$, $p<0.005$). Age, histology, the presence of "B" symptoms, performance status, previous RT or chemotherapy, the interval between ABMT and RT, the high dose regime used, and RT dose or field size, did not affect morbidity. Six patients remain progression-free 2-68 (median 15) months after RT.

RT may be useful after ABMT in patients with HD, but haematological toxicity may be expected in those with initial stage III or IV disease, particularly if extended fields are used.

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COMBINED ANTINEOPLASTIC AND ANTIRETROVIRAL THERAPHY FOR PATIENTS WITH HODGKIN'S DISEASE AND HIV INFECTION (HD-HIV): A PROSPECTIVE STUDY IN 17 PATIENTS.

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In an attempt to improve the results obtained with standard chemotherapy (CT) in HD-HIV and especially to decrease the occurrence of opportunistic infections (OI) during CT and follow-up observed in the retrospective evaluation of our previous experience, we designed a prospective combined antineoplastic and antiretroviral approach. Between March 1989 and March 1992, 17 consecutive previously untreated patients (median age 30 years) with stage III and IV, stage I and II, with adverse prognostic factors HD-HIV, were enrolled. The median CD4+ cell count was 184/mm^3. Patients were stratified in two groups and treated accordingly. Group A: patients with PS ≤ 3 and without OI received epirubicin 70 mg/m^2 iv d1, bleomycin 10 mg/m^2 iv d1 and vinblastine 6 mg/m^2 iv d1 (EBV); group B: patients with PS > 3 and /or OI in the history received a 50% reduced dose of epirubicin and vinblastine and a full dose of bleomycin. Courses were repeated every 21 days for six cycles. AZT was given at the dose of 500 mg/day per os from the beginning of CT in group B and after the third cycle in group A. Overall, 14 out of 17 patients showed an objective response (82%) and 9/17 (53%) achieved a complete remission (CR) with a median duration of 12 months. Toxicity was moderate with grade 3-4 leukopenia in 8 patients and grade 3 thrombocytopenia in 1 patient. Thirteen out of 17 patients received AZT as planned with a median duration of 9 months. We observed only one case of OI during or after CT with a median follow up of 10 months. We observed no worsening of HIV markers during the combined therapy, the median CD4+ cell count before and after therapy being 184/mm3 and 203/mm3 respectively. The median survival was 10.3 months with an actuarial survival of 43% at 36 months. The estimated disease free survival at 36 months is 66%. The median survival for the 9 CRs is not reached at the time of this analysis. In conclusion, these results revealed the feasibility and the activity of the combination of EBV regimen and AZT. Objective response rate seems similar to that previously observed for our patients receiving standard CT but only one OI occurred, and this compares very favourably to the 16 OI observed in the 28 patients treated with standard CT and without AZT(6% vs 57%) in our previous experience. Therefore, it seems that the addiction of antiretroviral therapy to EBV decreased the occurrence of OI during CT or follow up. Supported by grants of Airc '92.