5. Hodgkin's Disease

HALF THE PATIENTS WITH EXTRANODAL HODGKIN'S DISEASE REFRACTORY TO FRONT LINE CHEMOTHERAPY ARE PROGRESSION FREE AFTER 5 YEARS FOLLOWING A BEAM AUTOTRANSPLANTATION.

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Introduction: Extranodal Hodgkin's disease has been recognised as an unfavourable prognostic sign especially for patients who fail to remit with conventional chemotherapy. High dose therapy with autologous marrow or peripheral blood stem cell rescue has been widely proposed for this group of patients.

Patients and Methods: We have analysed 77 patients in our institution who underwent autotransplantation for extranodal disease refractory to conventional treatment. Patients characteristics: 39 males (51%), 38 females (49%); Histology: 61 nodular sclerosis (79%), 13 mixed cellularity (17%), 3 lymphocyte predominant or depleanted (4%); Stage at diagnosis: I and II 50 patients (39%), II and IV 47 patients (61%); 11 patients underwent splenectomy around the time of diagnosis. Disease location: 45 patients pulmonary involvement, 13 hepatic, 7 bone marrow, 9 more than 2 sites, 5 patients other sites. The response of these patients to chemoradiotherapy was as follows: 13 patients (17%) were in first partial remission, 5 patients (6%) showed progression within a month of stopping chemotherapy, 3 patients (4%) initially responded but then progressed before the completion chemotherapy and 56 patients (73%) either progressed or failed to achieve even a partial remission. All patients received BEAM chemotherapy.

Results: At 3 months following the transplant 32 patients (42%) attained a CR, 26 patients (34%) attained a PR and 11 patients (14%) showed no disease response. The overall progression free survival at 3 years was 50% and 45% respectively.

Conclusions: We conclude that BEAM therapy and autotransplantation appears to be an effective treatment option in patients with CT evidence of extranodal disease refractory to conventional chemotherapy. Patients with extranodal disease have a better outcome than patients with extranodal disease in other locations.

HIGH DOSE THERAPY (HDT) AND AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR ADULTS WITH HODGKIN'S DISEASE (HD) WHO FAIL TO ENTER REMISSION AFTER INDUCTION CHEMOTHERAPY (CT): RESULTS IN 175 PATIENTS (PTS) REPORTED TO THE EBMT.

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Only 10% to 15% of patients (pts) with HD who fail induction therapy achieve long term survival with conventional dose salvage therapy. Recent studies have shown superior results in patients with advanced disease receiving HDT and ASCT. Between Nov 1973 and Oct 1995, 175 adult pts with HD failing to enter remission after induction chemotherapy, for whom complete data sets are available, were reported to the EBMT, from 69 European centres. Induction failure was defined as either progressive disease (PD) or stable disease/minimal response (SD/mR) (n=57, 50%) to 2nd line chemotherapy. Pt characteristics at presentation: male - 100, female - 75; median age - 26.6m (17m to 55m); stage I+II - 1, III - 58, III - 55, IV - 55, N/A - 4; B symptoms 12; marrow - 10; mediastinum + - 133, disease bulk >5cm - 104. Induction: CHOP, MOPP, or ABVD-like - 59, MOPP/ABV or variant - 93, MOPP/ABV hybrid or variant - 10, others - 13; median no of cycles of 1st line therapy = 6 (1 - 12). Response to 1st line CT: PD - 88 (50%), SD/mR - 87 (50%). 5pts received HDT & ASCT after failure of induction regimen. 100pts received 2nd line CT. Median no of cycles of 2nd line CT = 3 (1 - 9). Response to 2nd line CT: PD - 14, SD/mR - 64. Results: response to HDT & ASCT: CR - 30%, PR - 28%, NR - 14%, PD - 14%, toxic death - 14%. Actuarial 5 year OS and PFS = 36% and 32% respectively. In univariate analysis for PFS and OS, adverse prognostic factors were: use of a 2nd line CT regimen (p=0.01 for PFS & OS; p=0.001 for OS & PFS; p=0.01 for PFS & OS; p=0.03 for OS & PFS); presence of extranodal disease (p=0.02 for OS; p=0.07 for PFS). In multivariate analysis, interval between diagnosis and ASCT retained significance for OS (p=0.02). Response to CT regimen prior to ASCT had no predictive value. Conclusions: HDT and ASCT is an effective strategy for patients with HD who fail induction therapy is equivalent for pts with PD and with SD or minimal response to prior therapy. Prospective studies are required to confirm its superiority over conventional dose salvage.

A randomised controlled trial (SNGL HDIII) of non-ablative autotransplant versus further chemotherapy in patients with very poor risk Hodgkin's disease. S.Proctor, F.Taylor; M.Mackie, B.Bang, F.Jack, J.White on behalf of the Scotland & Newcastle Lymphoma Group.

Introduction: Patients eligible for this study had an SNGL prognostic index of 0-5, (indicating a 45% chance of 4 year survival for non-radiated patients) and have a minimum of 12 months follow-up (median 54 months). All patients received treatment with an intensive 12 week continuous programme (PVACHEOP): Chlorambucil 5mg/m2 po days 1-14; Procarbazone 100mg/m2 po days 1-14; VP16 100mg/m2 iv day 1, 200mg/m2 po days 2-21; Vinblastine 10mg iv day 1; Adriamycin 25mg/m2 day 8; Vincristine 2mg iv day 8; Bleomycin 10mg iv day 15 and 22; Prednisolone 40 mg po days 15-28. No growth factors were given. Septalin prophylaxis was recommended for all patients. Complete pancytopoenia occurred rescheduling of drugs was written into the protocol rather than stopping treatment. After PVACHEOPx2 (12 weeks) those patients in CR/GPRB were eligible for randomisation. Radiotherapy to bulk disease was allowed. Patients received 2 further months of chemotherapy or autotransplant with Melphalan/VP16 conditioning. (Melphalan 3mg/kg, VP16 1.6 g/m2).

Results: 105 patients, 46F/59M; 49 Stage IV, 23 Stage III, 33 Stage II, of 105 patients eligible on H&E review; 70% had nodular Sclerosis histology; 22% immunohistochemistry; 8 patients were excluded. The regimen was routinely given on an out-patient basis. There was 1 death on treatment due to toxicity. Only 59 patients accepted randomisation and results in both arms are the same, (82% - 80% respectively). Patients not randomised were also allowed to elect further chemo or autotransplant. The results in these patients are also identical. The programme of treatment utilising PVACHEOP (equivalent dose intensity per month) and Melphalan/VP16 is very intensive and treatment in the poor risk HD group leads to increased cure rate. In this randomised trial further chemotherapy was equivalent to autotransplant. Overall survival (5 years) for those confirmed to have HD was 76%. Secondary leukemias has not been seen in trial patients.

IPOFAMIDE (I), CARBOPLATIN (C) AND ETOPOSIDE (E) (ICE) CYTOTOXICATION FOLLOWED BY HIGH DOSE CHEMORADIOLOGY AND ASCT FOR REFRUCTORY AND RELAPSED HODGKIN'S DISEASE (HD): AN INTENT TO TREAT STUDY.


Introduction and methods: A comprehensive prospective sequential second-line protocol for chemotherapy-refractory (21) and relapsed (44) HD was tested in 65 patients over 6 years. Fifty-four of the 55 ICE responders underwent ASCT. At a median follow-up of 27 months (11 to 53 months), the intention to treat event-free survival (EFS) of the entire group was 59%+7%. The EFS of the transplanted patients was 65%+7% who received CTA; the 2 patients included in all analyses. Cox regression analysis identified that presence of B symptoms or extranodal disease prior to ICE chemotherapy predicted for poor EFS. Patients with neither adverse factor had an EFS of 83% (24/29), 1 factor - 59% (14/24), and both factors - 8% (1/12). Conclusions: ICE is a safe, effective, non-stem-cell toxic chemotherapy program that when compared with CTA provides a higher overall survival in heavily pre-treated patients with HD. The strategy of combining ICE cytotoxication with intensive radiotherapy and high dose chemotherapy has yielded excellent results in patients with < 2 poor prognostic factors. Our prospective study also confirms that ICE is feasible and more effective for patients with those adverse prognostic factors.
SIX CYCLES OF ABVD IN THE TREATMENT OF STAGE I AND II HODGKIN'S Lymphoma (HL): FIVE-YEAR RESULTS.

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Introduction: ABVD is the standard treatment in advanced HL. However, until 1997 there were no published data with ABVD alone in adult patients (pts) with early HL. In 1997, we published the preliminary results obtained with ABVD chemotherapy in stage I and II HL (Clin Oncol 15: 1118-1122). In this abstract we update the results with more pts included.

Methods: Pts diagnosed with HL were staged with physical examination, hematological and biochemical tests, CT scan of the chest, abdomen and pelvis, and bone marrow biopsy. All pts with stage I or II were treated with six cycles of ABVD (standard doses), 9 pts with mediastinal bulky disease (MBD) criteria also received radiotherapy (RT) to the mediastinum.

Results: From January 1990 to December 1998, 56 pts were included (6, too early, are excluded from present analysis). Pts characteristics (absolute number): Age, median 29 years (16-75); sex, 26 male/24 female; stage I 110 II 40; MBD, 9; symptoms, 13.

For all (56) pts received more than 90% of planned dose. Toxicity was moderate; only 4 pts developed febrile neutropenia and in no case were RBC or platelet transfusions required. 1 pt developed grade 3 skin toxicity after the first dose, and was treated with another chemotherapeutic regime for 6 cycles (he is included in the outcome analysis). Clinical cardiopulmonary toxicity (acute or chronic) has not been observed.

After six cycles, 44 (88%) complete remissions (CR) and 6 (12%) partial remissions, which became CR, after RT, were obtained. All pts without MBD were in CR after ABVD. With a median follow-up of 12 months (22 pts have been followed for more than 5 years), 4 pts have relapsed; 2 of them are disease-free (2 and 4 years) after salvage treatment and 2 have died. Five-year actuarial progression-free and overall survival are 91 and 95%. For stage I, 2, or II pts without MBD, five-year actuarial progression-free and overall survival are 96 and 95%.

Conclusions: Six cycles of ABVD are effective and safe in stage I and II HL.

ASSESSMENT OF THE RISK OF BREAST CANCER FOLLOWING HODGKIN’S DISEASE: THE EFFECTS OF TREATMENT, AGE AT TREATMENT, ATTAINED AGE, ATM HETEROZYGOSITY, AND SELECTION BIAS.

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Introduction: Recent studies have consistently shown that the relative risk (RR) of breast cancer following Hodgkin’s disease (HD) strongly increases with younger age at radiation treatment. The RR of breast cancer after HD treatment before age 20 vary greatly in the literature (range 16 to 458). Part of this variation may be due to incorrect estimation of age at radiation treatment, age at treatment, attained age, genetic predisposition and selection bias on breast cancer risk.

Methods: The risk of breast cancer was assessed in 1253 patients diagnosed with HD before age 40 and treated between 1966 and 1986. The median follow-up time was 14 years. A simulation analysis was conducted to examine the effect of incomplete follow-up on risk estimation. In a nationwide case-control study, we collected blood samples of 30 patients with breast cancer following HD and 120 matched controls, to investigate whether individuals heterozygous for a germline mutation in the ATM gene have a greatly increased risk of breast cancer.

Results: In all, 27 breast cancers were observed (RR=5.2, 95% CI 3.4-7.6). Among female 15-year survivors first treated at ages ≤20, 21-30 and 31-39, the RRs were 1.6, 6.0 and 1.7, respectively. The 25-year actuarial risks of breast cancer were very similar (about 16%) in the 3 age groups. Among patients first treated before age 20, the RR of developing breast cancer at ages 40-49 was significantly lower than the RR of a breast cancer diagnosis before age 40 (RR=5.4 vs RR=62), suggesting that the strongly increased RRs in patients treated at a young age may decrease as they grow older. Salvage chemotherapy was associated with significantly decreased breast cancer risk, possibly related to premature ovarian failure. So far, we have found 10% ATM heterozygous mutations in patients with breast cancer. Thus, ATM mutations do not appear to play a major role in breast cancer following HD. The simulation analysis showed that a difference of 3 years in completeness of follow-up between breast cancer patients and healthy survivors can cause a 2-fold difference in calculated risk. The huge variation in reported risks in the literature will be put into perspective.

INTERIM RESULTS FROM THE ONGOING EORTC RANDOMISED TRIAL ON INVOLVED-FIELD RADIOTHERAPY IN STAGES III/IIV HODGKIN’S LYMPHOMA AND THE IMPACT OF THE INTERNATIONAL PROGNOSTIC SCORE.

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Introduction: The role of involved-field radiotherapy (IF-RT) in patients with stages III/IIV Hodgkin’s disease (HD) who reach a complete remission (CR) with MOPP/ABV chemotherapy, is being studied in the ongoing randomised EORTC trial 20884. Overall interim results and the impact of the international prognostic score on the outcome of patients are presented.

Patients and Methods: Previously untreated patients with stages III/IIV HD ≤70 years of age are eligible for entry. All patients receive 6-8 cycles MOPP/ABV chemotherapy. Patients in CR are then randomised between IF-RT (nodal areas 24 Gy) and no RT. Patients in partial remission after 6 cycles all receive IF-RT (nodal areas 30 Gy). The international prognostic score consists of seven adverse prognostic factors: age ≥45, male, Ann-Arbor stage IV, serum albumin <40 g/l, HD <6.5 mm/ml, hoarseness ≥15/1001, lymphocytes ≤8% of leukocyte count.

Results: As of January 1999, we have enrolled 666 patients from 8 European countries. The median age of the patients is 36 yrs, 63% of them being males. Stage IV disease is present in 43% of the patients; bulky disease (210 cm or MT-ratio ≥2.5) in 40%. Randomisation between IF-RT and no RT has been performed already in 291 patients. No data on outcome according to randomisation are yet available. Overall, 559 patients are evaluable for analysis of outcome after treatment. Sixty-one percent of the patients reach a CR with MOPP/ABV. Treatment failure (relapse, progression, or death due to other causes) is diagnosed in 15% of the patients. The 5-year overall survival probability is excellent with 84% (95% CI 79-87%). Patients with a prognostic score of 0 (0-2 adverse factors present) have a 5-year cumulative probability of treatment failure (CPTF) of 18% while those with a score of 3 have a CPTF of 32% (p<0.006).

Conclusion: In this ongoing randomised study, interim results show a favourable outcome for patients with stages III/IIV HD. The international prognostic score appears to fall in identifying a group of patients with a particularly poor prognosis.

TREATMENT OF ADVANCED HODGKIN’S DISEASE WITH ALTERNATING MOPP/ABV CHEMOTHERAPY FOLLOWED BY RADIOTHERAPY ON BULKY OR RESIDUAL DISEASE: LONG-TERM ANALYSIS OF EFFICACY, TOXICITY AND PROGNOSTIC FACTORS.

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Introduction: This paper analyses the long-term results of therapy in a series of 200 consecutive patients affected with advanced Hodgkin’s disease (stages IIb, IIIA-B and IV) and treated in a single institution from 1962 to 1995, with a median follow-up of 108 months. We evaluated the impact of pretreatment variables, adjuvant radiotherapy and drug dose-intensity on final outcome as well as long-term toxicity, with emphasis on fertility and occurrence of a subsequent neoplasia.

Methods: Alternating MOPP/ABV chemotherapy (ICR) and radiotherapy was administered in an 8-month program. Adjuvant radiotherapy (RT) was delivered in 49 patients, 25 of them had bulky mediastinum at presentation and 24 had residual disease after CT. Statistical methods included survival analysis and logistic regression for the candidate prognostic variables. Gonadal function was assessed in women by menopause and hormonal tests, most of young men had their semen cryopreserved.

Results: Complete remission (CR) rate after CT was 72%, histology other than nodular sclerosis, bulky mediastinum, B symptoms and hemoglobin (Hb) <12 g/dl, were significant adverse factors. The final CR rate after adjuvant RT was 82% with B symptoms and Hb <12 g/dl as adverse factors. Ten-year RFS and FFP were 79% and 63%, respectively, and overall survival was 72%. The presence of >2 extranodal sites and Hb <10 g/dl significantly worsened RFS and FFP, while OS was adversely influenced by histology other than nodular sclerosis (p=0.03), bone marrow involvement (p<0.006) and B symptoms (p=0.0003). No significant association was found between drug dose-intensity and final outcome. Grade 3 (WHO grading) acute hematologic toxicity occurred in 3% of cases, with no life-threatening episodes. No episodes of cardiac and/or pulmonary failure occurred. Acute leukemia or tumors developed in 2 and 6 cases, respectively. Fertility was preserved in young women and 9 cases of normal pregnancy were registered.

Conclusion: Alternating MOPP/ABV chemotherapy and adjuvant RT, when appropriate, cured more than 70% of patients with advanced Hodgkin’s disease; adjuvant RT was instrumental in achieving CR in patients with mediastinal bulky disease at presentation and residual disease after CT. Organ toxicity and carcinogenic risk were moderate; fertility was preserved in young women.
ChIPPP ALTERNATING WITH PABIOE IS SUPERIOR TO PABIOE ALONE AS INITIAL TREATMENT FOR ADVANCED HODGKIN'S DISEASE: RESULTS OF BRITISH NATIONAL LYMPHOMA INVESTIGATION (BNI)/CENTRAL LYMPHOMA GROUP (CLG) RANDOMISED, CONTROLLED TRIAL
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Purpose: A randomised trial was set up to compare the efficacy of six cycles of prednisolone, Adriamycin, doxorubicin, bleomycin, vincristine (Oncovin) and etoposide (PABIOE) with three cycles of PABIOE alternating with three cycles of chlorambucil, vinblastine, procarbazine and prednisone (ChIPPP).

Patients and methods: Between October 1992 and April 1996, 679 patients were entered into the study. 37 of these (10%) were excluded from further analysis, most of these being reclassified as NHL on histological review. Of the remaining 642 patients, 322 were allocated to receive PABIOE and 320 to ChIPPP/PABIOE.

Results: The complete remission (CR) rates were 79% and 64%, for ChIPPP/PABIOE and PABIOE respectively after initial chemotherapy (<p<0.001). Patients were re-evaluated subsequently following radiotherapy to residual masses. The CR rates changed from 79% to 87% for ChIPPP/PABIOE and from 64% to 75% for PABIOE when re-evaluated in this manner (treatment difference still significant, p<0.001). The treatment associated mortality in the PABIOE arm was 2.2% (7 deaths), whereas there were no such deaths in the ChIPPP/PABIOE arm (p=0.15).

The progression free survival was significantly greater for ChIPPP/PABIOE (<p<0.001) as was the overall survival (p=0.01). The progression free and overall survival rates at 3 years were 77% and 91% respectively in the ChIPPP/PABIOE arm, compared with 59% and 85% in the PABIOE arm.

Conclusion: ChIPPP alternating with PABIOE is superior to PABIOE alone as initial treatment for advanced Hodgkin's disease.

THE IMPACT OF SOLUBLE LEYDIG CELL DYSFUNCTION FOLLOWING CYTOTOXIC CHEMOTHERAPY ON BIOLOGICAL QUALITY OF LIFE. SJ Howlett1, JA Radford2, RMA Smets1, JH Strafe1, GR Margersten1, and SM Hegarty1,2,3,4,5
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The deleterious effect of orchidectomy on Leydig cell dysfunction is not unequivocal. The Leydig cells are sensitive to the toxic effects of chemotherapy. Whilst the germinal epithelium is more susceptible to damage than the Leydig cells, there is evidence of mild Leydig cell dysfunction in a proportion of men following treatment. Overt testosterone deficiency is associated with reduced bone mineral density (BMD), alterations in body composition, increased mood and reduced sexual function, but the impact of mild hypogonadism has not previously been studied. We have identified 36 men with mild Leydig cell insufficiency, defined by a raised LH level (LH > 3 IU/L) with a testosterone level in the lower half, or just below the normal range (testosterone 10-30 nmol/l), following cytotoxic chemotherapy (CT) for haematological malignancy. All subjects were 20-55 years old, and were in stable remission a median of eight years following treatment with conventional high-dose chemotherapy and R-MOD (measured by dual-energy x-ray absorptiometry (DXA) and quantitative CT (QCT), body composition (measured by DXA), and quality of life were assessed in all, and the results compared with 14 age-matched controls who had undergone the same CT but had entirely normal hormone levels. Mood was assessed using the hospital anxiety and depression scale (HADS), sexual function using a modified version of a questionnaire used in trials of the male contraceptive pill, and fatigue using the multidimensional fatigue inventory (MFI-20).

When data from all 36 men was considered together, there were significant reductions in mean BMD at the lumbar spine for both DXA and QCT measurements (p<0.04, p<0.01. QCT; z=-1.5, p<0.0001) and at the femoral neck (DXA; z=-0.5, p<0.001). Mean femoral neck BMD was significantly lower in patients compared with controls (z=-0.68 vs z=-0.11, p<0.05) and there was a trend towards lower lumbar spine BMD (z=-1.64 vs z=-1.10, p<0.05). There was a trend towards lower lean body mass (58.6kg vs 60.4kg; p=0.06) and a higher percentage fat (25.3% vs 24.0%; p=0.04) in the patients compared with the controls, and there was a difference in the distribution of fat body with a propensity for the patients to accrue truncal fat (trunk fat; 25.5% vs. 23.7%, p=0.03; ratio of truncal fat to non-truncal fat; 1.05 vs. 0.90; p=0.02).

There was a trend towards higher anxiety scores and reduced sexual activity in the patients compared with the controls (mean anxiety score 7.4 vs 6.1; p=0.35 sexual activity score 1.8 vs 1.31; p=0.05). Mean anxiety score was higher than previously reported in normal men. Fatigue scores were significantly higher in both the patients and controls compared with a cohort of normal healthy men. There were no significant differences in any of the fatigue scores between the patients and controls, but those patients who had received XRT had significantly higher scores than those who had not. These data suggest that patients may have clinically significant effects on BMD, body composition, mood and sexual function, although it is not yet clear whether these changes are the cause or the consequence of treatment. Estrogen replacement may be beneficial in some of these men and this requires further evaluation.

ChIPPP alternating with PABIOE is superior to PABIOE alone as initial treatment for advanced Hodgkin's disease.

BCL-2 IS FREQUENTLY EXPRESSED IN HODGKIN-REED-STERNEBerg CELLS AND IS ASSOCIATED WITH INFERIOR FAILURE-FREE SURVIVAL IN HODGKIN'S DISEASE TREATED WITH ABVD
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Objective: Hodgkin-Reed-Sternberg cells (HRSC) are B-cells with rearranged Ig loci, and they express intracellular proteins that would be expected to cause apoptosis. Since bcl-2 may protect cells from apoptosis, we decided to determine the frequency of bcl-2 expression in HRSC and its relationship to FFS in HD. Methods: FFX with confirmed HD from MD Anderson and Instituto Tumori were included in the diagnostic review. Reactive and viable HRSC were identified in formalin-fixed paraffin embedded tissue sections using the APAAP (avidin-biotin-peroxidase) complex method. In each case, the frequency of bcl-2 expression was recorded. Results: Of the 52 cases tested, 76% had detectable levels of bcl-2. When compared to patients with bcl-2 expressing HRSC, those with HRSC without detectable bcl-2 had significantly shorter FFS and OS (p<0.001). Conclusion: Bcl-2 expression is an independent predictor of survival in HD and should be included in the routine staging workup.

LACK OF ACUTE HAEMATOLOGICAL TOXICITY DURING CHEMOTHERAPY CORRELATES WITH REDUCED DISEASE CONTROL IN ADVANCED HODGKIN'S DISEASE
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Introduction: Patients with advanced Hodgkin's Disease (HD) differ considerably in acute haematotoxicity when treated with the same chemotherapy regimen. The degree of haematotoxicity may be indicative of the integrity of the immunological and metabolic potential. Assuming a dose outcome relationship, we suspected that low haematotoxicity might correlate with reduced disease control.

Patient and Methods: 266 patients with advanced HD treated with COPP/ABVD (HDLSG I and HDLSG II, 1983) were included in the study. The WHO-grade of leukopenia was overpassed in an observation the chemotherapy cycles given and was weighted with the reciprocal dose intensity (DI) of the corresponding cycle. The low toxicity group was defined as having an averaged WHO grade of leukopenia ≤2. The independent impact of low haematotoxicity on freedom from treatment failure (FFTF) was assessed multivariately including the international prognostic score for advanced HD. The results were validated in two independent cohorts (n=181 patients treated with COPP/ABV in the HDLSGIII, n=250 patients treated with COPP/ABV/IMEP in the HDLSG IV).

Results: The 5yr FFTF rates are 68% for patients with high toxicity vs 47% for patients with low toxicity (multivariate relative risk (RR) 2.0, p=0.0002). This finding is not an artefact due to early deaths or progressions not subject to cumulative toxicity (analysis restricted to the patients n=224 with full chemotherapy). Multivariate RR 1.7, p=0.03).

Patients with low toxicity had significantly higher DI than patients with high toxicity (p=0.02) and dose intensity (p=0.0001). The effect of low toxicity was confirmed in the two validation cohorts (p=0.001 resp. p=0.01).

Conclusions: Patients with low acute haematotoxicity have significantly higher failure rates. This observation is consistent with the hypothesis that haematotoxicity mirrors the effective dose given. If confirmed, a strategy of individualized haematotoxicity adapted dose escalation should be explored.

5. Hodgkin's Disease
2 CYCLES ABVD PLUS RADIOTHERAPY IS MORE EFFECTIVE THAN RADIOTHERAPY ALONE IN EARLY STAGE HD - RESULTS OF THE HD7 TRIAL OF THE GHSG


Introduction: Extended field radiotherapy is effective in patients with early stage HD and more than 90% reach a complete remission. However, up to 25% eventually relapse and have to be treated with intensified polychemotherapy. Low dose neo-adjuvant chemotherapy may reduce the risk of relapse and improve treatment results.

Methods: 640 patients in stage I and II without clinical risk factors (large mediastinal mass, massive spleen involvement, extranodal disease, elevated ESR > 3 lymph node areas) were enrolled in the HD7 trial and randomized as follows: A: Extended field radiotherapy with 30 Gy, involved field with 40 Gy, spleen with 36 Gy. B: 2 cycles ABVD (Adriamycin, bleomycin, vindesin, dacarbazine) followed by the same RT as in A. Both groups were well balanced for age, sex, histological subtype and stage.

Results: The median follow up time of this interim analysis, which is restricted to those patients randomized before 12/96 is 22 months. 365 out of 407 pat. were evaluable. The CR rate was 96% in arm A and 98% in arm B (ns), 6 pat. (3%) progressed during therapy in A and 1 pat. in B (p=0.005). Kaplan-Meier estimates of freedom from treatment failure (FFTF) showed a significant difference with 87% vs. 96% at 24 months. The difference is mainly due to the reduced number of relapses in B (one relapse vs. 17 in arm A). Survival rates are not different (97% vs 98% at 24 months). Of 12 deaths 2 were due to HD, 3 due to acute toxicity during radiotherapy. Two pat. died during salvage therapy and one from MDS/AML. Acute toxicities WHO/CTC were rare (nausea 8.6%, pharynx 3.5%, esophagus 3.3%, leukocytosis 2.9%). 9 pat. developed secondary tumors including 1 NHL, 1 AML and 7 solid tumors.

Conclusions: The interim analysis demonstrates that neo-adjuvant chemo-therapy with 2 cycles of ABVD significantly reduces the rate of relapses and improves FFTF. Current trials with combined modality therapy aim to reduce acute and long-term toxicities by reduction of radiotherapy dose and volume.

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INVOLVED FIELD RADIATION IS AS EFFECTIVE AS EXTENDED FIELD RADIATION FOLLOWING CHEMOTHERAPY FOR INTERMEDIATE STAGE HD: A RANDOMIZED STUDY


In intermediate stage Hodgkin's disease (HD) treatment results with combined modality treatment are excellent. Reduction of radiotherapy volume seems to be possible without loss of treatment results.

To investigate whether Involved Field (IF) is as effective as Extended Field (EF) irradiation after a standard chemotherapy regimen in intermediate stage Hodgkin’s disease. In this analysis 742 patients recruited between 1/93 to 10/96 by the GHSG for the HD-8 trial with first diagnosis of HD were included. Patients with CS I/II and at least one risk factor (large mediastinal mass, massive spleen involvement, extranodal disease, elevated ESR or ≥ 3 lymph node areas involved) and CS/III Aa without risk factors were randomized to receive 2 cycles of COPP/ABVD and either 30 GY EF plus 10 GY Bulk or 30 GY IF plus 10 GY Bulk. Of 742 patients 651 were eligible for arm comparison, 34 patients have been withdrawn because of progressive disease (16), death (4), excessive toxicities (2) and others (12) while CT. Patients characteristics were distributed equally between both arms. With a median follow-up of 26 months there was no differences in complete remission rate (98%/98%), survival (97%/97%) and freedom from treatment failure (EF 94%/IF 91%). The rate of the certain WHO grade 1-3 toxicities were significantly increased in the IF irradiation arm. This analysis suggests that the reduction of radiotherapy volume is possible in intermediate stage Hodgkin’s disease without decline in treatment results. This leads to a considerable advantage for the patient by shortening duration and decreasing the intensity of treatment. Whether this reduction will affect long term side effects remains to be seen.

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LOCALISED HODGKIN'S DISEASE (HD) WITH RADIOTHERAPY ALONE (RT) AND COMBINED MODALITY THERAPY (CMT)

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Introduction: Localized HD is a highly curable disease. However, in spite of effective treatment, a small proportion of patients still dies of disease. We assessed the PMH experience in the past decade to look at factors predisposing for death from HD.

Methods: Of 479 patients (pts) with stage I and II HD with a median age of 29 yrs (range 15-82) treated between 1987-1996, 207 received RT alone, 233 CMT and 40 CT alone. Median follow-up was 5 yrs (range 0.5-11.4). 76% had nodular sclerosis HD, and 95% presented with supradiaphragmatic disease. Stage IA-1A2 pts, IIA-2A5 pts, II B-12 pts, III B-88 pts.

Results: The 5-yr overall survival, cause-specific survival and disease free survival were 93%, 95% and 80% respectively. Although 76 pts failed the initial, only 21 pts died of HD. In univariate analysis B-symptoms (<0.0001), large mediastinal mass (LM) (0.035), anemia (Hb<10.0) (0.0003), and age >50 yrs (<0.0001) predicted for death of HD. In multivariable analysis, presence of LM (RR 3.4), and anemia (RR 4.5) were associated with a higher risk of death (p<0.05).

Conclusions: More aggressive treatment strategies should be considered for patients with early stage HD presenting with a large mediastinal mass and unexplained anemia as these patients are at significantly higher risk of early death from HD.

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OUTCOME OF PATIENTS WITH HODGKIN-LIKE B CELL LYMPHOMAS FOLLOWING TREATMENT DESIGNED FOR HODGKIN'S DISEASE

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We have reevaluated 255 biopsies from consecutive adult patients with Hodgkin’s disease (HD) diagnosed 1985-1994. The purpose was to identify and characterize patients with Hodgkin-like B Cell Lymphomas (B-NHL) primarily diagnosed as HD. The morphology and the immunophenotyping were reviewed and, when necessary, new immunostainings for CD15, CD30, CD20, LN-1, CD79a, CD3, UCHL-1, EMA, κ and λ were performed.

Results. Reclassification to B-NHL was done in 16 cases (6%): 12 T-cell-rich B-NHL; 3 large cell B-NHL and 1 primary mediastinal B-NHL. Initially these cases were classified as lymphocyte predominant (LPHD, 4), nodular sclerosis (NS, 4), mixed cellularity (MC, 6) and lymphocyte depletion (LD, 2). There were 12 males and 4 females with a median age of 40 years (range 20-77); stage I (6), stage II (3), stage III (4) and stage IV (3). Five patients had B symptoms. Six patients were treated with chemotherapy alone, 8 with MOPP/ABVD or similar chemotherapy and 2 with combined modality treatment. Thirteen patients (81%) achieved CR on front-line therapy, remaining 3 patients were refractory to treatment and died from progressive disease. Four patients have relapsed, one of whom is alive in third CR.

At follow-up the remaining 9 patients were in continuous CR for 42 to 134 months (median 74 months). Patients with B-NHL did not differ significantly from remaining patients with regard to sex, age, stage, bulky disease, extra-nodal disease, bone marrow infiltration, splenomegaly, B-symptoms or remission and relapse rate. The overall survival was significantly worse in patients with B-NHL compared to patients with LP (<0.05) and NS (<0.05) but not MC (<0.27).

Conclusion. Immunohistochemical studies make it possible to identify cases of B-NHL morphologically difficult to distinguish from classical HD. The results suggest that ‘conventional’ treatment for HD induces CR in HD-like B-NHL at a rate comparable to that in HD patients. The low response rate in relapse may explain the worse overall survival in this B-NHL population.
LONG-TERM RISK OF GASTRO-INTESTINAL MALIGNANCIES IN YOUNG SURVIVORS OF HODGKIN'S DISEASE. B.M.P. Alkema, W. J. Klozim, A. D. Grof, M. B. van 't Veer, E. A. Welp, F. E. van Leeuwen, The Netherlands Cancer Institute, Amsterdam, the Netherlands, The Dr. Daniel den Hoed Cancer Center, Rotterdam, the Netherlands.

Introduction: Although increased risk of gastro-intestinal malignancies has been observed in several studies, the risk has hardly been evaluated by type of treatment, follow-up time and age at first treatment for Hodgkin's disease (HD).

Methods: The risk of GI cancers was assessed in 1,253 patients diagnosed with HD before the age of 40 between 1966 and 1986. The median follow-up time was 14 years. The clinical characteristics and treatment of the patients who developed stomach cancer have been studied in detail.

Results: In all, 26 patients developed a gastro-intestinal second cancer (GI SC), versus 3.1 expected (relative risk RR = 8.4, 95% confidence interval 5.3-12.3). The actuarial 25-year risk of GI SC was 6%. Significantly increased RR were observed for cancers of the esophagus (RR = 30.6, 95%CI 9.9-71.4), stomach (RR = 10.9, 95%CI 4.4-22.6), rectum (RR = 7.0, 95%CI 3.3-16.4) and liver (RR = 40.1, 95%CI 8.5-117). The absolute excess of GI cancers ten years after treatment exceeded the excess number of cases per 10,000 persons per year, was for GI SC overall 1.4, for esophagus cancer 3.0, for stomach cancer 3.6, for rectum cancer 2.6 and for liver cancer 1.8. The RR of GI malignancies strongly increased with longer follow-up time, up to a RR of 12 (95% CI 5-22) in 20-year survivors. The RR of GI increased strongly with younger age at first treatment with a RR of 36 (95%CI 1.4-74) for patients treated at the age of 20 or before. Treatment with chemotherapy (CT) for relapse was associated with significantly higher risk of GI cancer than radiotherapy (RT) alone (RR = 13 versus RR = 1.3).

All patients who developed stomach cancer had been treated with a combination of abdominopelvic RT and long-term CT during primary or salvage treatment. All patients presented with an advanced stage of stomach cancer. 50% of the patients underwent a partial gastrectomy, 37.5% were treated primarily with CT and 25% received CT because of a recurrence. After a median follow-up time of 6 months after diagnosis of stomach cancer only one patient was still alive.

Conclusion: The absolute risk of GI SC is of moderate size for patients treated for HD before the age of 40. In the follow-up of long-term survivors of HD special attention is needed for early symptoms of GI tumors, especially stomach cancer.

TREATMENT OF PATIENTS WITH PRIMARY PROGRESSIVE HODGKIN'S OR HIGH-GRAD NON-HODGKIN'S LYMPHOMA - IS THERE A CHANCE OF CURE?

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Purpose: Although modern combination chemotherapy for non-localized Hodgkin's (HD) and high-grade non-Hodgkin's lymphoma (h-g NHL) can be curative for 30-75% of patients, those with no response or only partial response to first-line treatment have a poor prognosis. We retrospectively analysed patients with primary progressive h-g NHL and HD who were treated at our institution with different salvage regimens. Patients who failed to achieve a complete remission (CR) after induction treatment, with progressive disease during induction treatment or those with transient response (<90 days) to induction treatment were defined as progressive disease.

Patients and Methods: 131 pts with primary progressive lymphoma (h-g NHL; n = 64; HD; n = 67) were available; the median age was 42 years (range 18-68). Patients with progressive lymphoma ≤ 60 years were eligible to receive high-dose chemotherapy with autologous stem cell support (ASCT) if they reached a PR or CR after salvage chemotherapy. Pts with h-g NHL were treated with different regimens including ICE (n=18), DTZ (n=12), B-ALL-protocol (n=11), DEXA-BLUM (n=8) or DHLAP + HEDEST (n=15). Pts with progressive HD were treated with DEXA-BLUM (n=61) or DHLAP + HEDEST (n=6).

Results: The overall response rate after salvage therapy for pts with primary progressive h-g NHL was 15%. Only 6 pts (9.6%) with primary progressive h-g NHL received HDCT. Mean overall survival for pts with h-g NHL after first diagnosis and after entry into the salvage protocol was 13.7 months and 6.8 months, respectively. No patient survived longer than 26 months. In contrary, patients with primary progressive HD had an overall response rate of 33% after salvage chemotherapy. 24 pts (36%) received HDCT. Overall survival OS after 5 years was 19% for all patients with HD. The OS after 5 years for pts with primary progressive HD who received HDCT was 52% vs 0% for patients who were not transplanted due to chemoresistant disease.

Conclusions: The prognosis of patients with primary progressive h-g NHL is dismal. Most patients had rapid progressive disease after salvage treatment and were therefore excluded from HDCT programs with ASCT. For patients with progressive HD after induction treatment who were chemosensitive to conventional salvage therapy long-term surviving can be observed after HDCT.

DO BIOLOGICAL MARKERS ADD TO PREDICTION OF OUTCOME ACHIEVED BY MULTIVARIATE INTERNATIONAL, SCORE IN HODGKIN'S DISEASE?

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Background: Factors predictive of progression-free and overall survival following multiagent chemotherapy in advanced stage Hodgkin's disease (HD) have recently been identified by an International Prognostic Factor Study. This prognostic score is also relevant for HD patients with limited disease. However, the discriminatory power of this score does not allow classification of a distinct group of patients with a very poor outcome who may benefit from aggressive upfront treatment. Objective: To define biological factors which may add to the international score in predicting outcome of previously untreated patients with HD.

Patients and methods: One hundred and forty-nine patients (>15 years; 84 males, 65 females) with HD diagnosed 1974-1992 were included. Their median age was 36 years (range 14-87); stage I (n=38), stage II (n=48), stage III (n=33) and stage IV (n=30). Fifty-eight patients had HD symptoms. Histology was lymphocyte predominance in 12, nodular sclerosis in 78, mixed cellularity in 53, lymphocyte depletion in 1 and unclassified in 5. Seventy-three patients were treated with radiotherapy alone, 57 with MOPP/ABVD or similar chemotherapy and 19 with combined modality treatment. Median follow up for surviving patients was 143 months (range 28-272). Apart from factors included in the international score, routine chemistry, serum levels of sCD4, sCD8, sCD25, sCD30, sCD54, interleukin (IL)-10, beta 2-microglobulin and thymidine kinase were analysed as well as spontaneous and concanavalin A induced blood lymphocyte DNA synthesis (lymphocyte function). Results: The following variables significantly predicted cause specific survival in univariate analysis; serum sCD30, lymphocyte function, hemoglobin, albumin (p<0.001); lymphocyte count, serum IL-10, age (p<0.01); stage (p<0.05). Conclusion: Serum levels of sCD30 and IL-10 and lymphocyte function were the strongest biological predictors of prognosis. Multivariate analysis of these and clinical prognostic factors will be presented.

5. Hodgkin's Disease
6. High Dose Therapy

Phase II/II Feasibility Trial of Rituximab Following High Dose Chemotherapy and Autologous in B-Cell Non-Hodgkin’s Lymphoma

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Introduction: High dose therapy with autologous grafting increases the events-free survival in aggressive non-Hodgkin’s lymphoma (NHL) However, 40-60% of patients relapse. As most malignant lymphomas express the CD20 antigen, rituximab is an excellent candidate for additional therapy in the post transplant setting. It has independent anti-tumor activity and has shown linkage toxicity. The purpose of our study is to evaluate the safety and efficacy of rituximab after autologous peripheral blood stem cell transplant (APSBT).

Methods: We treated 6 patients with recurrent or refractory aggressive B-cell NHL unresponsive to APBSCT. Each patient’s preparative regimen was BCNU, Cyclophosphamide, and Etoposide. Patients then received 4 weekly infusions of Rituximab at 350mg/m² starting at day+0 after transplant. In addition to evaluating toxicity, lymphocyte subsets, immunoglobulins, and immune response to vaccinations are measured. Results: Of the 6 patients treated thus far there have been 3 instances of grade 2 hypotension and one instance of grade 2 vomiting during the infusion. 3/6 patients have developed neutropenia (see table). 5/6 patients developed grade 4 lymphopenia. One case of herpes zoster is the only infection noted in the post treatment period. 1/6 patients have relapsed with a mean follow-up of 4 months.

Time s/p PBSC

Rituximab Treated

<table>
<thead>
<tr>
<th>Time s/p PBSC</th>
<th>Neutropenia</th>
<th>Historical Controls</th>
<th>Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 60</td>
<td>Medium</td>
<td>2.19</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.93–5.72</td>
<td>1.8–7.2</td>
</tr>
<tr>
<td>Day 120–150</td>
<td>Medium</td>
<td>1.12</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.55–2.37</td>
<td>1.3–3.3</td>
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</table>

Conclusion: In preliminary results, rituximab infusion is well tolerated. We have unexpectedly seen neutropenia in 3/6 patients. This same incidence of neutropenia has not been observed in other NHL patients undergoing the same preparative regimen and PBSC. These episodes have all resolved without clinically significant complications. Induction therapy has not been a significant problem. Effects on immune reconstitution and efficacy are being studied. While rituximab following autologous PBSC has been generally well tolerated, the unexpected incidence of neutropenia suggests that further phase II data be collected before undertaking large phase III trials.


Introduction: FL are sensitive to a variety of chemotherapeutic agents, however a continuous pattern of relapse is seen and there is little evidence that pts with advanced disease can be cured. The GETAMO Spanish Cooperative Group has carried out a retrospective study to know the role of high-dose therapy with ASCT.

Methods: From June 1987 to December 1999, 210 pts with FL underwent ASCT in Spain. The number of fl pts treated was 121, 120 pts with follicular large and small cell lymphoma, 17 pts with mantle cell, and 12 pts with mantle cell plus G-CSF. The median number of CD3+ cells infused was 3.12 x 10^8/kg (range 1.1 to 37). The conditioning regimen consisted of CTV in 53 pts. The remaining 157 pts were treated with BEAC (54 pts), BEAM (53 pts), CBV (12 pts) or BCU (2 pts) regimens.

Results: Response after transplantation was CR in 172 pts (82%), PR in 17 pts (8%) and failure in 10 (5%). The CR rate in CR1 pts (63 pts) were not available because they died before the 21st day post-ASCT. The median follow-up of the disease-free patients was 26 months. Thirty-seven pts have relapsed, the median time to relapse was 13 months (range 2 to 65 months). Estimated 10-year OS and DFS for all 210 pts was 50% and 43%, respectively, with a median GUS of 20 months. The actuarial probability of relapse for 172 evaluable pts was 41% at 10 years. In the univariate analysis, variables correlated with OS were disease status at ASCT (p<0.001), performance status at ASCT (p<0.004), bulky tumor at ASCT (p<0.005), B-2 monoclonality at ASCT (p<0.005), response to 1st line therapy (p<0.03) and B lymphomas at diagnosis (p=0.04). Multivariate analysis showed that the presence of bulky tumors at diagnosis (p<0.000) and IP at diagnosis (p<0.000) were the only variables that retained their independent predictive value for OS Variables correlated with relapse in univariate analysis were performance status at ASCT (p<0.004), IP at diagnosis (p<0.004), disease status at ASCT (p<0.03), B lymphomas at diagnosis (p<0.03). In the multivariate analysis, disease status at ASCT (p<0.03) and IP at diagnosis (p=0.02) retained significance for relapse. The overall mortality was 18% (36 of 201). Sixteen pts (8%) died because of lymphoma and the remaining 20 (10%) as a result of toxicity. Toxicity mortality in 1st CR was 4%.

Conclusions: This large series shows that prognostic factors at diagnosis as well as disease status and PS at transplant influence the outcome of pts with FL submitted to ASCT.

HIGH-DOSE THERAPY WITH PERIPHERAL BLOOD STEM CELL (PBSC) SUPPORT IN PATIENTS WITH LOW-GRADE FOLLICULAR LYMPHOMA M.T. Vosotros, S. Martin, A. Abdallah, S. Hohaus, A. D. Ho, R. Haas* "Dep. Internal Medicine V, Heidelberg University and *German Cancer Research Center, Heidelberg, Germany.

Introduction: Follicular lymphoma (FL) is characterized by indolent clinical course and high-response rates to conventional therapy. Still, a significant number of patients relapse and some of them present with transformation to an aggressive, poorly treatment-responsive, large-cell lymphoma. The benefit of high-dose therapy with hematopoietic stem cell support for patients low-grade NHL is still controversial.

Methods: We treated 111 patients with advanced stage low-grade FL with high-dose therapy and PBSC support. Seventy patients were enrolled in first remission, whereas 41 were treated in second or higher remission. All patients were enrolled at best response following induction therapy, consisting of a median of 3 cycles of anthra- cycline-containing regimens. Twenty-one patients received radiotherapy as part of their induction. High-dose therapy consisted of total-body irradiation plus cyclophosphamide and of BEAM in 8 patients. Autografts contained 8.1 ± 0.6 x 10^6 CD34+ cells/kg BW (Mean ± SD). CD34-selected cells were transplanted in 15 cases.

Results: At a median follow-up of 44.2 months from PBSC, 93 patients are alive, with a probability of overall and relapse-free survival of 83% and 64%, respectively.

Conclusion: These results may support the concept that high-dose therapy with autologous concomitant fl use, however, is controversial. The benefit of high-dose therapy with hematopoietic stem cell support for patients low-grade NHL is still controversial.


While high dose therapy and PBSC transplant can produce durable disease free survival in select patients with NHL, many patients relapse after this procedure. Using a tumor specific monoclonal antibody may be one way to purify the stem cell graft in vivo and increase the efficacy of the preparative regimen. Rituximab as an IgG1 kappa chimeric mouse-human antibody fragment containing murine-human chimeric IgG1 kappa heavy and light chain variable region human kappa 1 heavy-chain and light-chain constant regions. The antibody reacts specifically with the CD20 antigen found on the surface of malignant and normal B-cells. We have conducted a trial of rituximab as an in vivo purging agent and as post-transplant adjuvant immunotherapy. Patients with NHL received 75 mg/m^2 of rituximab daily of mobilization, followed by cyclophosphamide 2.5 g/m^2, d4, and G-CSF 10 µg/kg starting d5. Stem cells were collected using a high volumepheresis procedure with a goal of 5 x 10^6 CD34+ cells/kg. The preparative regimen consisted of either cyclophosphamide and total body irradiation or busulfan and cyclophosphamide. G-CSF was used post-transplant. One dose of rituximab was given post-transplant 7 days after pts reach 20K. Twenty-five patients (15% of total), median age 50 range (32-65) have started therapy. Diagnoses include 10 FCC, 8 mantle cell, 5 AITL, 1 marginal zone and 1 Waldenstrom’s. 4/25 patients were successfully mobilized (median 1.07 x 10^6 CD34+ cells, range 2.5 x 10^6 - 9.5 x 10^6 CD34+ cells). No CD20+ cells were detectable by flow cytometry in any of the grafts. Seventeen of 23 patients required only one high volume apheresis. The median days ANC > 1000 was 10 (2-15) and unsupported platelet ≥ 20,000 was 9 (3-14) in 20 patients who have reached day 2+30. Toxicities include 1 patient who developed pneumonia starting at approximately day 30 and died day +232 of multisystem organ failure. Three patients have developed azotemia late after discharge. One patient developed ITP that rapidly responded to steroids. We conclude that this is a well tolerated regimen that successfully depletes stem cell grafts of CD20+ cells, provides rapid engraftment, and is associated with little added toxicity. The mobilization failure rate appears low, especially given these patients prior therapy with nucleoside analogues. Follow-up continues.
TANDEM TRANSPLANTATION, AUTOGRAFTING FOLLOWED BY MINI-ALLOGRAFTING, FOR RESISTANT HEMATOLOGICAL MALIGNANCIES AND METASTATIC BREAST CANCER.

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Introduction: We have recently demonstrated that immunosuppressive therapy alone is able to determine the engraftment of donor HPC and that autografting (ASCT) followed mini-allografting (m-ALLO) can be combined to achieve tumor bulk reduction after ASCT and the control of MRD after m-ALLO.

Methods: Our data refer to 18 advanced patients: Hodgkin’s Disease (8), Non-Hodgkin’s Lymphoma (2), Chronic Myelogenous Leukemia (2), and metastatic Breast Cancer (4). Two pts with RAEB were treated only with m-ALLO. In preparation for autografting, the patients underwent high-dose therapy on protocols appropriate for the underlying disease. At a median of 40 days after autografting of autologous HPC, all pts were conditioned for allografting with immunosuppressive agents alone (fludarabine 30 mg/m² × 3days) in 16 pts and cyclophosphamide: 300 mg/m² × 3 days (Fla-Cy protocol). Then, HLA matched donor HPC mobilized with G-CSF were infused to the patients. GVHD prophylaxis consisted of CSP and MTX.

Results: After ASCT, Lymphomas: CR 3, PR 6 and PD 1; CML: 2nd CR-CML in both pts; Breast cancer: all pts showed the reduction of tumor. After m-ALLO complete chimerism was achieved in 8/16 pts (50%) and mixed chimerism in other 6 pts (33%). Two pts are on evaluation only two pts were with BCP and RAEB appear to have had autologous recovery. Three pts had HD in CR after autografting maintained the remission after m-ALLO; 6 pts achieved CR after mini-allografting (HD; RAEB 1; AP-CMML; NHL). Eight of these 9 pts had achieved complete (4) or mixed (5) chimerism while one pt is on evaluation. Subsequently, the RAEB patient relapsed and 1 pt with HD died in CR. Two pts achieved a second CR after m-ALLO and 2 pts achieved CR following B-transplantation. Grade II-III aGVHD was the single major complication. In only two pts ANC decrease to <1x10⁹/l was reached. No patients required steroid.

Conclusions: Immunosuppressive therapy with matched sibling donor HPC without procedure-related deaths, moreover, we have demonstrated that the combination ASCT/m-ALLO can be pursued in a serious ill population and some of these pts achieved a remission.

HIGH DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION IN AGGRESSIVE NHL: ANALYSIS OF A RANDOMIZED MULTICENTER STUDY. U.Kaiser, U.Belackner, K. Havemann on behalf of the German high Grade Lymphoma study group, Marburg, Germany.

Between 3/1991 and 6/1997 312 patients with primary high grade NHL aged >60 having the risk factor serum LDH >normal level were included in a randomized multicenter study of the German high grade lymphoma study group. Pts either received 5 cycles of CHOP (cyc 750 mg/m², adria 50 mg/m², vcr 2 mg, etoposid 3x100 mg/m², pred 5x100 mg) followed by involved field (IF) radiotherapy [A] or 3 cycles of CHOP followed by autologous stem cell transplantation on BEAM followed by IF radiation [B] (in case of response after 2xCHOP). Pts were stratified according to age (<50), stage (IIA, IVA) and LDH (>400). First analysis was performed after a median observation period of 12 months; among 131 pts randomized to arm B, 67% received high dose therapy (HDT). In 14% HDT could not be performed due to lack of response after 2xCHOP. 39% of pts with HDT had stomatitis grade III and IV. Median duration of neutropenia (<500/µl) was 10 days, of thrombocytopenia (<20,000/µl) 11.5 days. Transplant-related mortality was 0, Estimated overall survival for the 312 pts is 64% after two years, 70% for arm A, 58% for arm B (log rank test). Comparing pts who received treatment according to the protocol 2-year survival is 75% in arm A and 73% in arm B. When pts were grouped according to the International Prognostic Index there was no survival benefit for any group in the high dose arm. Pts who died of relapse after HDT relapsed early with a median interval of 3 months after HDT. HDT was performed in a multicenter study without treatment related mortality. Estimated 2-years overall survival so far does not favor high dose therapy over conventional treatment. Relapse after HDT occurred early with median interval of 3 months. Further follow-up is awaited.

A EBMT SURVEY OF 671 CASES SUBMITTED TO AUTOLOGOUS STEM CELL TRANSPLANTATION FOR DIFFUSE LARGE B CELL LYMPHOMA. R. Fanin, M.C. Ruiz de Elvira, A. Spadoni, A.E. Goldstone, N. Tozer. For the EBMT Lymphoma Working Party. 'Dpt of Bone Marrow Transplantation, University Hospital Udine, Italy. 'University College London, UK. 'Dpt of Internal Medicine, University of Kiel, Germany.

Diffuse large B cell lymphoma (DLBCL) is an entity of REAL Classifications which includes histological subtypes like centrolblast (CB), immunoblastic (IB) and anaplastic large cell (ALC) lymphoma. It was recently shown that these subtypes have a distinct conventional chemotherapy. To confirm this in the context of autologous stem cell transplantation (ASCT), we are analyzing 671 cases of DLBCL reported with the EBMT Registry. As most of these patients were registered to the EBMT Registry before the introduction of the REAL classification, this project includes an histopathological review of all the cases. Herein we report preliminary data about the characteristics and outcome of these patients.

Patient characteristics at presentation: male - 60.5%, female 39.5%; median age at diagnosis 41.3 years; stage I - 8.5%, II - 24.0%, III - 20.0%, IV - 47.5%; B symptoms - 40.5%; bulky disease (size of largest mass >10cm) 37%; mediastinal involvement - 34.0%; bone marrow involvement - 18.0%; peripheral nodes involved - 76.0%; Source of stem cells: bone marrow - 52.5%; peripheral blood stem cell - 43.0%; both - 4.5%.

Patients characteristics at ASCT: age at transplant 43.4 years; 1st CR - 30.0%; ≥ 2nd CR - 19.5%; PR - 24.0%; relapse (R) refractory - 26.5%.

Conditioning regimen: chemotherapy alone - 84%; Response: 1 year OS and 2 year OS are respectively 69.7% (95% C.I. = 66% - 73%); and 59.5% (95% C.I. = 56% - 63%); 50% of patients are alive 5 years (95% C.I. = 46% - 54%)

Conclusions: these preliminary results do not seem superior to conventional chemotherapy but it must be underlined that the majority of the patients in this series were transplanted in advanced stage disease.

The aim of this retrospective study was to analyze the impact of several variables at transplantation in 366 patients with large cell lymphoma (LCL) who have received high dose therapy followed by bone marrow (BM) and/or peripheral blood stem cell (PBSC) support. At diagnosis, 258/366 patients (71%) had stages III-IV and bone marrow was involved in 21%. 216 (59%) had extramedullary disease; IPI was 3.4 in 38% of patients and 20% had a T phenotype. At transplantation, 129 patients were in first complete remission (CR), 63 in second CR and 144 had active disease (sensitive in 130 and resistant in 44). Conditioning regimens included: BEAM (134 patients), BEAC (130), CY * TBI (43), CY + BEAM (16), CY + TBI (23) and CY + BEAM (10). 38% of patients transplanted on CR or sensitive disease and 25% of those transplanted with resistant disease died due to the procedure. Regarding to the prognostic influence on overall survival (OS) and disease free survival (DFS) of the status at disease at transplantation, we have observed that patients in first CR displayed the best prognosis (estimated OS and DFS at 6 years 71% and 76% respectively), followed by those transplanted in second CR or sensitive disease (OS : 55% and 46% and DFS : 50% and 42%) and the worse outcome corresponded to patients transplanted with resistant disease (OS 4% and DFS 38%, p = 0.0003). Univariate analysis showed that eight disease characteristics at transplant (performance status, B symptoms, III-I stages, bulky disease, high LDH, extranodal sites (≥ 2), IPI and diagnosis status) had a significant influence on survival. On DFS, only IPI and status of the disease at transplant had a significant value. On multivariate analysis, the only independent prognostic factor with influence both on OS and DFS was the status at transplant. In summary, our retrospective analysis confirms the importance of the status of the disease at transplant as a determinant of result.

FURTHER HIGHER DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION IS NOT SUPERIOR TO CHOP REGIMEN FOR ADULT PATIENTS WITH NON-HODGKIN`S LYMHPHOMA: RESULTS OF A RANDOMIZED TRIAL BY THE GOELAMS.

N. MILPIED, E. DECONINCK, Ph. COLOMBAT, C. FOUSSARD, B. DESABLEANS, V. DELWAAL, C. BERTHET, C. JAUBERT, P. PASASSUS, L. LE TORCOTRE, C. LE MAIGNAN, M. MAISONNEUVE, JF. RAMEE, A. LEMEVEL, M. JARDEL, Ph. MOREAU and JL. HAROUSSEAU.

University Hospital, Tours - France

Introduction: CHOP remains the standard therapy for intermediate and high grade NHL. Non-randomized trials showed excellent efficacy of frontline high-dose chemotherapy with autologous transplantation (ABCT). Randomized trials have proved the superiority of ABCT in only in high risk high grade NHL. CHOP was randomized between CHOP (C = 750 mg/m2, H = 50 mg/m2) for eight courses every 21 days or high dose chemotherapy (HDC) consisting of two courses of DEX (C = 1.2 mg/m2, Etoposide 100 mg/m2, Vindesine 3mg/m2 or PDN) supported with GM-CSF, followed by a course of High dose Methotrexate (3 g/m2) with Cytarabine 100 mg/m2 d 5 CIv, PBSC were harvested after 1st and 2nd CECT in order to support 3 BEAM regimen (Etoposide 400 mg/m2 d, Cytaurabine 400 mg/m2 d CIv x 4) scheduled on d66 of 1st CECT.

Methods: In this trial pts age 15 to 60 years old with newly diagnosed and high risk age adjusted IPI intermediate or high grade lymphoma (NHL) were randomized between CHOP (C = 750 mg/m2, H = 50 mg/m2) for eight courses every 21 days or high dose chemotherapy (HDC) consisting of two courses of DEX (C = 1.2 mg/m2, Etoposide 100 mg/m2, Vindesine 3mg/m2 or PDN) supported with GM-CSF, followed by a course of High dose Methotrexate (3 g/m2) with Cytarabine 100 mg/m2 d 5 CIv, PBSC were harvested after 1st and 2nd CECT in order to support 3 BEAM regimen (Etoposide 400 mg/m2 d, Cytaurabine 400 mg/m2 d CIv x 4) scheduled on d66 of 1st CECT.

Results: Of 202 pts included, 167 (83 HSC, 83 HDC) are available at this time. Age 15-60 years old (median 47). Ann Arbor stage was II (with bulky abdominal disease) in 21%, III in 28% and IV in 50% of the pts. BM was pos in 28% of pts at Dg. According to age adjusted IPI, 11% of the pts were in the low 25% in the intermediate low, 48% in the intermediate high and 6% in the high risk category. Characteristics were matched between the two groups. With a median follow up of 12 m (1 to 3.5 y) the probability of survival at 3y is 64% (+/- 5%) with no difference between the two arms: 40 pts died, 38 of disease, 2 deaths were TTR related. The 3 y probability of EFS is 41% (+/- 6%) with no statistical difference between the 2 groups (CHOP : 41% ; HDC : 50%). The median time to relapse is 6 m (+/- 4 m) and the median time to response is 2 m (+/- 1 m).

Conclusion: Front line HDC including BEAM intensification is not superior to standard CHOP. Other strategies must be evaluated to improve on both survival and EFS.

FAILURE OF DOUBLE AUTOTRANSPLANT (DAT) AS FIRST LINE CONSOLIDATIVE TREATMENT IN POOR-RISK AGGRESSIVE LYMPHOMA: A PILOT STUDY OF 36 PATIENTS. C. Maun, D Simon, B. Queret, P. Huguet, C. Reau, G. Blessbrecht and F. Reyes for the GELA. Hospita I Heni Mondor, Creil, France.

Introduction: In the LNH87-2 study (JOQ 15:1133, 1997) we have shown that consolidative high dose chemotherapy (HDC) improves disease-free survival and survival for patients (pts) with 2 or 3 factors of the age-adjusted international prognostic index (AA-IPI) if they first reach complete remission after induction.

Methods: In order to improve further the outcome of such patients we conducted a pilot study of consolidative double autotransplant (DAT). The procedure consisted of 1 induction with 4 cycles of ACVe (P) in responding pts, peripheral blood stem cell (PBSC) collection with G-CSF after the fourth cycle of ACVe (16 pts) or after an additional regimen for mobilization (CTX 4.5 g/m2, VP16 450 mg/m2 + G-CSF) (17 pts) a 3 cycle of HDC (AT1) (Mitoxantrone 45 mg/m2, CTX 150 mg/m2 + 4x VP16 250 mg/m2 x 4 and BCNU 300 mg/m2) followed by PBSC rescue 4 a second cycle of HDC (AT2) (Busulfan 3.3 mg/kg x 4, Carboplatin 400 mg/m2 x 3 and Melphalan 140 mg/m2) with rescue.

Results: From 08/95 to 07/97, 39 pts under 60y were enrolled. Median age is 47y and the main characteristics were: O histologic group 77%, AA-IPI 3 factors 46%, marrow involved 35%, T-cell phenotype 18%. Response to induction was: CR 72% (28 pts), PR: 13% (5 pts), progression 8%, death 5%. Among the 33 responding pts, 32 AT1 were performed (because of cerebral thrombocytopenia in 1 pt). Median time to AT1 was 4 months. Three pts progressed after completing AT1 and 2 pts had insufficient PBSC collection: therefore AT2 was performed in 27 pts (median time AT1 to AT2 : 2 m). The toxicities included expected neutropenic fever and severe mucositis. The median day to recovery of 1000 ANC/m was 14 for AT1 (range, 8 to 26) and 13 for AT2 (range, 9 to 20). Platelets recovered to 20,000/mm3 at a median of 14 days for AT1 (range, 8 to 20) and AT2 (range, 9 to 20). Survival at 2 years was 30% for AT1 and 27 pts who completed DAT, pts died from treatment-related toxicity (VOD in 2 cases and cerebral toxoplasmosis in 1). In addition, 2 pts experienced difficult mycobacteriosis infection and 1 pt Extravascular retnitis. 8 pts progressed (2 to 13 months after AT2) and 6 of them died. At the time of analysis, 16 pts are in continuous CR. With a median follow-up of 26 months, 27 pts and survival are 42% and 52%, respectively.

Conclusions: We conclude that the DAT procedure does not improve outcome of these high-risk pts, as compared to the results of the LNH87-2 study in which such pts received a single consolidative AT. These results led the GELA to stop this pilot study.
PHASE II TRIAL OF A SALVAGE THERAPY BY DHAP PLUS HIGH DOSE CHEMOTHERAPY AND TOTAL BODY IRRADIATION (TBI) WITH AUTOLOGOUS STEM CELL TRANSPLANTATION (SCT) AFTER FAILURE OF CHOP REGIMEN FOR MANTLE CELL LYMPHOMA (MCL)


Introduction: MCL is a well-defined entity among low grade lymphomas that is characterized by a unique Burkitt immunophenotype, is not well classified. Although most of the published series of patients (pts) with MCL have used anthracycline-containing regimens, the prognostic remains poor with a short median survival. We have conducted, in a homogeneous group of untreated pts with MCL, a phase II trial to assess: 1. The efficacy of CHOP and consolidation with high dose therapy and ASCT 2. The interest of DHAP as salvage treatment in non-responding pts, followed by ASCT with Ara-C containing regimen.

Methods: The diagnosis of MCL was based on the morphology of lymph nodes, immunophenotypic, cytogentic and molecular biology. All pts received a 6 cycle CHOP regimen. CR: complete response, PR: partial response ≥ 50%, MR: minor response < 50%. Failure was defined by progression or death. Responses to treatment was assessed after 4 cycles: pts in CR or PR had PBSC mobilization after Cytoxan (Cy) (4.5 gm2), VP16 (450 mg/m2) and G-CSF. Response was evaluated after PBSC mobilization. CR was maintained after a conditioning regimen with CY (120 mg/kg) and TBI. Pts who did not reach CR after CHOP and CYVP16 mobilization regimen were treated with 4 cycles of DHAP. Then, ASCT was performed after a high dose Ara-C containing regimen (TAMM): Methotrexate (140 mg/m2), Ara-C (8 mg/m2) and TBI (12 Gy).

Patients: 20 pts with MCL were included. Median age 53 years (40-61). All of the patients were classified as stage IV.

CR PR MR failure
65% 43% 23% 6%

No complete remissions were obtained after 6 cycles (one death from septic complications). The overall survival (OS) was 81% at 15 years. ASCT was performed in 15/17 pts. 16 pts/17 are still alive (13 pts in CR, 2 in PR, 1 progression) after a median follow-up of 22 months (10-45).

Conclusion: The preliminary result confirms that anthracycline-based regimen is not able to reduce CR in MCL, whereas high dose DHAP significantly increases CR rate. Moreover, ASCT with TAMB regimen is feasible with an acceptable toxicity. Follow-up is too short to conclude on its efficacy on CR duration. These data suggest that the results of this study are not generalizable as first line therapy in MCL. A longer follow-up are warranted to confirm our results.

EARLY AUTOLOGOUS STEM CELL TRANPLANTATION AS FIRST-LINE THERAPY IN POOR PROGNOSIS NON HODGKIN'S LYMPHOMA (NHL): AN ITALIAN RANDOMIZED TRIAL


Purpose: To evaluate the role of an early intensification with High Doses and Autologous Stem Cell Transplantation (HDASCT) as front line chemotherapy in poor prognosis lymphomas, high risk NHL, with unfavorable prognostic factors.

Methods: We planned a multicenter randomized trial with the aim to compare a conventional chemotherapy (MACOP-B) (arm A) versus a short course of MACOP-B (8 cycles) followed by HDASCT using BEACOM (arm B).

Results: 25 patients were randomized in arm A and 25 pts in arm B. In arm A, all patients, an involved field radiotherapy (36Gy) was delivered on site of the bulky disease. There were no statistical differences in terms of sex, mean age, clinical symptoms, performance status, bulky disease and DLBCL between the two groups.

Conclusions: The results of this trial showed that HDASCT seems superior to conventional chemotherapy. Our major problems have been the high number of pts not addressed to transplant procedure. This study is still ongoing, additional pts and follow up will be needed for definitive results.


Introduction: Pts with MCL have a poor response to chemotherapy with a continuous pattern of relapse, which means that these patients are not cured. The GELTAMO Spanish Cooperative Group has established a retropective study to know the role of high-dose therapy with autologous stem cell transplantation (ASCT).

Methods: From December 1988 to December 1997, 25 pts with MCL underwent ASCT. The morphological and immunological diagnosis was supported by histochemistry and immunohistochemistry analysis on tissue sections and/or cell suspensions by flow cytometry. Median age was 49 years (range 21 to 64) and 39 pts were male. Pts were treated as first line therapy with CVP (4 pts), CHOP (35), ProMACE-CytaBOM (8), Hyper-CVAD (6) and DHAP (2) Disease status at ASCT was CR in 1 pt, second CR in 9 pts, chemosensitive disease in 28 pts and chemoresistant disease in 3 pts. Stem cells for engraftment were obtained from bone marrow in 22/38 or from peripheral blood in the remaining 45. In order to mobilize PBSC 29 pts received G-CSF and the remaining 16 chemotherapy plus G-CSF. The median value of CD34+ cells infused was 3.29x10^6/kg (range 1.2 to 3.3). The conditioning regimen was cyclophosphamide and total body irradiation in 12 pts. The remaining 43 pts were treated with BEAC (19 pts), BEAM (16 pts), CBV (6 pts) or BUCY (2 pts) regimens.

Results: Response after transplantation was CR in 44 pts (80%), PR in 7 (13%), failure to treat 2 (4%) and the other 2 (4%) were not evaluable because they died before the 21st day post-ASCT. The median follow-up of the disease-free pts was 17 months. Sixteen pts have relapsed, the median time to relapse was 12 months (range 3 to 30 months). Estimated 9-year DFS and EFS for all 55 pts was 38% and 26%, respectively, with a median DFS of 16 months. The actuarial probability of relapse for 44 evaluable pts was 67% at 4 years. The major prognostic parameters associated with a short DFS (≤ 1 year) were at diagnosis at ASCT p<0.04. No predictive factor of a higher probability of relapse was found. Median time to granulocyte (≥ 0.5 x 10^9/l) and stable platelet (≥ 20 x 10^9/l) recovery was 12 and 14 days, respectively. Median time to discharge was 19 days. Sixteen pts (29%) died. Toxic mortality was 24% and mortality due to lymphoma was 24%. No pts transplanted in CR died due to toxicity.

Conclusions: The results presented here show a high remission rate with a significant relapse rate for patients with MCLs treated with ASCT.
BENEFIT FROM CONSOLIDATION WITH HDT DURING ICR IN ADULTS WITH LYMPHOMAS AND BURKITT'S LYMPHOMA

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Introduction: Chemotherapeutic regimens with several non-cross-resistant agents, and CNS prophylactic are the standard induction treatments for patients with lymphoblastic and Burkitt’s lymphoma. For patients reaching CR1, it is unresolved whether consolidation with high dose chemotherapy with stem cell support (HDT) yields results superior to those from treatments with other chemotherapeutic regimens. The present study investigates this question.

Methods: From 1983 to 1989 patients referred to our institution with lymphoblastic and Burkitt’s lymphoma were treated with CHOP, high dose methotrexate (MTX), and intrathecal MTX, and if reaching a 1 CR - consolidated with CHOP. From 1989 we changed our treatment strategy, so that patients with disease stage I-II B aged 15-55 years who reached CR instead of CHOP received HDT consolidation with high dose cyclophosphamide and total body irradiation. Treatment modalities and other prognostic features in patients fulfilling the criteria for HDT referred before and after 1989 were compared in an univariate and multivariate analysis on an intention to treat basis. Endpoints were overall survival (OS) and disease free survival (DFS).

Results: Forty-nine patients were identified. Twenty-two patients were treated before 1989. Following induction therapy altogether 33 patients (67%) reached CR, off those 11 were treated before 1989. There were no prognostic variables for reaching a CR. The estimated 5-year overall survival for all patients was 49%. B-symptoms (odds ratio=2.94) and response to induction chemotherapy (odds ratio=0.02) were found to be independent prognostic variables for OS. For the 33 patients in CR following induction chemotherapy the DFS was 66%. DFS was significantly improved from 36% to 82% with the introduction of HDT consolidation. Cox multivariate analysis revealed that HDT (odds ratio 0.24) was the only significant variable predicting DFS.

Similar results were obtained using OS as endpoint.

Conclusion: This retrospective analysis suggests that consolidation with HDT in CR improves survival in patients with advanced LBL and BL.

TEN YEAR RESULTS WITH HIGH-DOSE SEQUENTIAL (HDS) CHEMOTHERAPY AND PBPC AUTOGRFT IN LYMPHOMA: OVERALL TOXICITY AND LONG-TERM OUTCOME


Introduction: Since 1989 we have extensively employed the high-dose sequential (HDS) chemotherapy regimen, in its original or modified versions, in the management of high-risk lymphoma. We here report our experience long a decade on the HDS programs.

Methods: The original HDS includes sequential administration of hd-cyclophosphamide (CY) followed by PBPC harvest, methotrexate, etoposide (VP16) and then submyeloablative treatment with PBPC autograft, an intensified version has been recently developed including the addition of ara-C following CY: a modified HDS for low-grade NHL includes 2 APO + 2 DHAP courses, and inversion of CY to VP16 sequence, in order to collect PBPC after prolonged debulking. G-CSF is always given at 5 μg/kg/day following hd-drugs. So far, 181 pts. (126 at disease onset, 55 at relapse) entered HDS programs. Median age was 45 yrs. (range 16-65), M/F ratio 111/70, histology included 79 low/intermediate grade, 87 intermediate/high grade NHL, 15 relapsed HD.

Results: There were 8 (4%) toxic deaths (5 in the hd-phase, 3 after autograft); 4 more pts. developed a second malignancy. All pts. had short-lasting fever, oral mucositis and needed transfusion support. Severe infections or organ complications occurred in a minority of cases. At a median follow-up of 3.6 yrs. (range 1-9), 102 pts. are alive without disease progression, and the median DFS has not been reached at a median follow-up of 3 yrs.

Conclusions: HDS program may be widely employed in lymphoma pts., with a treatment-related mortality similar to that of conventional regimens; its use in high-risk pts. is associated with prolonged survival.

UP-FRONT HIGH-DOSE THERAPY AND AUTOLOGOUS PERIPHERAL BLOOD PROGENITOR CELL TRANSPLANTATION VERSUS STANDARD CHOP CHEMOTHERAPY IN POOR PROGNOSIS AGGRESSIVE NON-HODGKIN’S LYMPHOMA: A PRELIMINARY REPORT

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Objectives: To compare the effectiveness of high-dose therapy (HDT) and peripheral blood progenitor cell transplantation (PBPC) administered up-front with standard CHOP chemotherapy in adult patients newly diagnosed with poor prognosis (high- and high-intermediate risk groups by aged adjusted international prognostic index) aggressive non-Hodgkin’s lymphoma (NHL). Category P, G, H by the Working Formulation.

Methods: Fifty-eight patients, aged 15-55 years, were enrolled. Sixty-five percent were high-risk patients and 78% had diffuse large-cell lymphoma. After three courses of CHOP, patients were stratified randomized according to age, risk-group and degree of tumor bulk into two arms, one with CHOP or switch to ESHAP followed by HDT and PBPC and two or four courses of ESHAP were given as indicated by the degree of tumor response at randomization. All analyses were made on the basis of intention-to-treat.

Results: Nine patients (15%) died during the first three cycles of CHOP and one patient was lost to follow-up. Twenty-five patients were assigned to receive CHOP and 23 HDT. The rates of complete remission were 48% and 36% in patients treated with HDT and CHOP, respectively (P=0.56). At a median follow-up of 12 months, the patients given HDT, as compared with those treated with CHOP, had significantly higher rates of freedom from disease progression (64% vs. 25%, P=0.008) and freedom from relapse (91% vs. 37%, P=0.05) at 3 years. The event-free survival was also significantly different which favored the patients treated with HDT (33% vs. 13%, P=0.05). The overall survival at 3 years however did not significantly differ between the two groups (34% vs. 32%, P=0.83). While relapse and progressive disease (PD) was the major factor for treatment failure in patients treated with CHOP (71%), the main cause of failure in patients given HDT were severe febrile neutropenia (39%) and disease relapse or progression (49%).

Conclusions: HDT and PBPC reduce the risk of disease relapse and progression as compared to CHOP therapy in patients newly diagnosed with poor prognosis aggressive NHL. A more vigilant supportive care for the associated febrile neutropenia may further improve the overall survival of the patients. (Supported in part by grant from Roche, Thailand)