1334 ORAL

Breast cancer (BC) after cured Hodgkin's disease (HD)

B. Cutuli[1], C. Borel[1], F. Dhermain[2], S.M. Magrini[3], Th. Wassermann[5], J.A. Bogart[5], M. Provencio[4], B. de Lafontan[2], A. de Larochefordiere[2], Y. Graic[2], P. Kerbrat[2], C. Alzieu[2], E. Teissier[2], J.M. Dilhuydy[2], H. Mignotte[2], M. Velten[1]. [1]*Centre Paul Strauss, Strasbourg, France;* [2]*Other French;* [3]*Italian;* [4]*Spanish;* [5]*American Centers, United States*

Purpose and Methods: We report 119 women treated for HD between 1960 to 1988. The median age at diagnosis of HD was 24 years; 74 women (62.2%) received exclusive RT, and 45 had previous CT.

Results: The 119 women developed 133 BC. The median interval between HD and BC was 15 years. DIC represents 81.6% of the cases, but pure DCIS was found in 10.4% of the cases, and other types in 8%. Among the infiltrating carcinoma the axillary involvement rate was 53.4%.

Mastectomy was performed in 77 cases, and lumpectomy without or with RT in 12 and 32 cases. Four others were treated exclusively by RT, five by CT and one only by Tamoxifen; 18 (15.1%) patients developed local recurrence and 41 (34.5%) metastases.

The five-year disease-specific survival rate is 61% (pN0: 91%, pN1–3: 66%, pN > 3:0%)

Conclusion: Our study define two types of secondary BC: one very agressive with high rate of lymph node involvement and the second more favourable, with often DCIS subtype and with a longer "latent period".

Consequently, the young women treated for HD should be carefully monitored, especially by mammography. For these secondary BC a conservative treatment in sometime feasible.

1335 POSTER DISCUSSION

Towards the most intensive group CHOP regimen for high-grade non-Hodgkin's lymphomas (NHL)

A. Santoro, F. Latteri, M. Balzarotti, H. Soto Parra, P. Salvini, G. Brambilla, V. Ginanni, G. Biancofiore, R. Bufalino. *Istituto Clinico Humanitas, Rozzano-Milano, Italy*

Background: as previously reported (ASCO, 1997), it has been possible to increase of almost two times the dose-intensity of CHOP by utilising G-CSF.

Methods: in order to further increase the DI and dose-size of both doxorubicin (ADM) and cyclophosphamide (CTX) a second study was undertaken in 20 pts with high grade NHL. The dose of ADM was fixed at 75 mg/m^2, like in the previous study, while the dose of CTX started at 1750 mg/m^2 and was increased of 250 mg/m^2 in cohorts of at least 3 pts in the absence of dose limiting toxicity (DLT). G-CSF was given s.c. at 300 μcg/m^2 from day 7 to day 12. Cycles were restarted every 2 wks instead of the classic 3 wks. DLT was considered as either grade IV neutropenia > 7 days, or grade III thrombocytopenia $\geq$ 7 days or any grade IV thrombocytopenia, or non-haematological toxicity other than alopecia.

Results: DLT was observed in 3/4 treated pts at 2250 mg/m^2 of CTX. Relative (RDI) and Actual received Dose Intensity (ADD) at 1750 and 2000 every two wks were compared to MTD of 2750 mg/m^2 every 3 wks of the previous study.

CTX mg/m^2	pts n	wks	*CTX:* RDI	ADI	*ADM:* RDIA	ADI
Standard CHOP		3	1		1	
2750	7	3	3.7	3.59	1.5	1.49
1750	9	2	3.5	3.39 (2.86–3.61)	2.25	2.18 (1.84–2.33)
2000	7	2	4.0	3.35 (2.01–4.06)	2.25	1.92 (1.54–2.25)

Conclusion: according to these data the dose level of 1750 mg/m^2 with doxorubicin 75 mg/m^2 every two wks must be considered as the most intensive CHOP regimen. This schedule is safe to administer on an outpatient basis.

1336 POSTER DISCUSSION

Analysis of efficacy and long-term toxicity in the treatment of early-stage Hodgkin's disease with four cycles of ABVD followed by limited radiotherapy

A. Baio[1], P. De Vecchi[1], P. Franchini[1], E. Brusamolino[2], F. Lunghi[2]. [1]*I.R.C.C.S. Policlinico San Matteo, Radioterapia Oncologica, Pavia;* [2]*I.R.C.C.S Policlinico San Matteo, Ematologia, Pavia, Italy*

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

Methods: Seventy-eight patients, with median age of 33 years (range 15–64), were included in a prospective study: 20 with clinical stage I and 58 with stage II; 6% had B symptoms, 5% subdiaphragmatic disease, 60% had mediastinal enlargement and 12% bulky disease. The median follow-up was 56 months. The treatment program consisted of 4 cycles of standard chemoterapy (ABVD regimen), followed by standard RT to involved sites in 44 patients, or to involved and contiguous sites of disease in 34 patients; RT total dose ranged from 30 to 36 Gy to uninvolved and involved sites, respectively; bulky disease received a boost up to 44 Gy. Gonadal function was assessed in women by ormonal tests and menses evaluation. An estrogen-progesteron combination was used in fertile women, for ovarian protection, while most of young men had their semen cryopreserved.

Results: The whole treatment program was reached in a median of 6.2 months (range 5–9.8). The complete remission (CR) rate, achieved after 4 ABVD in 69 patients was 88%, 98% after the adjunctive RT. The 5-year relapse free-survival (RFS) is 97%; two of the 3 relapsing patients reached only a partial remission after ABVD chemotherapy. The 5-year overall survival is 98%; two patients die: one of disease progression and one of a small cell lung cancer. Long-term toxicity included pulmonary fibrosis with symptomatic interstitial disease (2 cases), one case of dilated cardiomyopathy with cardiac failure (all patients had received mediastinal irradiation), and hypothyroidism requiring replacement therapy in 5 cases. Fertility was preserved in young women and four normal pregnancy were registered. No cases of secondary leukemia occurred.

Conclusion: The combination of a short CT regimen with 4 cycles of ABVD and limited irradiation was effective and produced 97% RFS at 5 years, in early stage Hodgkin's disease patients without staging laparatomy. A prolonged monitoring of potential long-term sequelae of therapy and evaluation of their impact on quality of life are mandatory in this curable setting of patients.

1337 POSTER DISCUSSION

Salvage chemotherapy for Hodgkin's disease – A seven-drug containing regimen with and without stem cell transplant

M. Rahal, S. Bazarbashi, A. El-Weshi, M. Raja, C. Pai, M. El-Foudeh, A. Al-Sayed, A. Ezzat, D. Ajarim, E. Ibrahim. *KFSH&RC, Riyadh, Saudi Arabia*

Purpose: Between 1993 and 1997, 38 PTs with relapsed or refractory Hodgkin's Disease were given salvage chemotherapy with Etoposide, Solu-Medrol, Cytarabine and Platinum (ESAP) alternating with Ifosfamide, Methotrexate and CCNU (IMC) q.28 days.

Material: M/F:26/12; median age: 21 years; range: 14–60. initial stage: IB:1 PT, IIA/IIB:2/3, IIIA/IIIB:3/7, IVA/IVB:3/19. Pathology: NS:22, MC:11, LP:4, unknown:1. Bulky mediastinum:13 Patients (PT). Initial chemotherapy: MOPP/ABV(D):24, COPP/ABV(D):6, MOPP:5, ABVD:1, other:2. Initial radiation in 11 PT. Response to previous chemotherapy: NR:2; PR:14, CR < 1 year:14; CR > 1 year:8. Visceral involvement in 23/38 PT, and 13 had B symptoms. Number of prior regimen: 1:28; 2:6; 3:4. Number of relapses: 1:24; 2:9; 3:5. Median number of cycles of salvage given 5 (1–8).

Results: 34 evaluable PT. NR:11; PR:6; CR:17. Starting January 1996 all responders (below 60 years) of age underwent high dose chemotherapy and stem cell transplantation. 14 PT have been transplanted, 12 with PBSC (1 combined with ABMT), 1 ABMT, 1 allogenic. With follow-up ranging from 12 to 36 months, 8 PT of the transplant group are alive NED (5 were in CR after ESAP/IMC, 2 in PR, 1 NE). 3 are alive with disease and 3 died (2 PD, 1 from toxicity). Among 20 PT treated with ESAP/IMC only and with a follow-up from 24 to 72 months, 5 PT are alive NED, 3 alive with disease and 12 died.

Conclusions: ESAP/IMC is an effective regimen in the salvage of Hodgkin's Disease.

1338 POSTER DISCUSSION

Anthracyclin-related leukaemias after breast cancer (BC) adjuvant/neoadjuvant treatment: Dose relationship?

S. Delaloge[1], E. Cvitkovic[1], P. Cottu[2], J.L. Misset[1]. [1]*Hop Paul Brousse;* [2]*Hop Saint Louis, France*

Secondary acute leukemias (SAL) related to anthracyclins used in the neoadjuvant/adjuvant treatment of BC are an emerging major concern.

These Topoisomerase-II inhibitors-type leukaemias display specific clinical and cytogenetic characteristics, such as short latency (median 18 months), monocytic phenotype and specific translocations. The potential relationship between dose, dose-intensity, pharmacological interactions with other drugs, and incidence of those SAL is yet undetermined.

Mat. and Methods: the data of 8 international phase III trials (7383 patients (pts), median follow-up 37–160 months) informative for anthracyclin-related SAL have been reviewed. The doses of anthracyclins used can be classified as low (Dox $\leq$ 50 mg/m^2/cy or 4-Epi $\leq$ 50–60 mg/m^2/cy, 1211 pts) or high (Dox $\geq$ 60 mg/m^2/cy or 4-Epi 100–120 mg/m^2/cy, 6172 pts).

Results: the observed anthracyclin-related SAL numbers regarding doses used are listed in the following table.

	Low doses Dox/4-Epi	High doses Dox/4-Epi
Total Nb Pts	11211	6172
Nb anthra-related SAL	1 (0.08%)	$\geq$26 ($\geq$0.4%)

These simplified data strongly suggest a dose-response relationship of anthracyclin-related leukemogenesis, which should be studied in a multifactorial model. Since early BC pts are more and more likely to receive high anthracyclin doses, a concerted and/or prospective effort is warranted to resolve these issues.

1339 POSTER

Survival analysis of an additional therapy with oral enzymes in patients with multiple myeloma

A. Sakalova[1], L. Dedik[2], P.R. Bock[3], J. Hanisch[3], W. Schiess[4]. *[1]Clinic of Haematology and Transfusion Medicine, University Hospital, Bratislava; [2]Faculty of Mechanical Engineering, Slovak Technical University, Bratislava, Slovakia; [3]IFAG Basel, Basel, Switzerland; [4]MUCOS Pharma, Geretsried, Germany*

The objective of this study was to assess existing data on patients with Multiple Myeloma (stages I–III) treated with different therapeutic regimens – Chemotherapy alone (VMCP/MOCCA, VAD) (CH) vs. Chemotherapy and additional treatment with oral enzymes (Wobe-Mugos® E, MUCOS Pharma, Geretsried, Germany) (OE). For this a retrolective cohort analysis in parallel groups of data of all patients diagnosed and treated in the Clinic of Haematology and Transfusion Medicine, Bratislava, from 1987 to 1997 (CH 99, OE 166 patients) was performed. Aim of this analysis was to investigate the effect of OE on survival. Primary efficacy parameter was the Kaplan-Meier-estimate of survival and the median survival time for both groups. Secondary parameters were response quality and response rate during the first year, duration of first remission, and the safety of a treatment with OE.

Both groups were comparable for their demographic data, and also for disease specific data. In the OE group for disease stage III median survival was 83 months compared to 47 months in the CH group (P logrank = 0.0014), and also for stages I–III survival time was longer in the OE group; adjusted sample (P logrank = 0.0003). In stage IIIA the resp. results were 88 vs. 49 months (P logrank = 0.0040), and for patients with renal insufficiency (stage IIIB) 66 vs. 37 months (P logrank = 0.1460). Multivariate Cox regression analyses confirmed these results. Response rates are higher and duration of remission is longer in the OE group. An early remission and a long duration of the first remission is an important prognostic factor for the survival of the patient.

Oral enzymes were well tolerated with 3.6% of the patients experiencing mild to moderate gastrointestinal symptoms.

The long term additional therapy with oral enzymes in patients with multiple myeloma receiving optimised chemotherapy regimens considerably prolongs survival. In our group of 265 patients median survival prolongation depended on disease stage, and on therapy with/without OE. Progression of disease stage increases the estimated mortality risk 5 to 6 fold, whereas OE decrease the estimated mortality risk by 50 to 60%.

1340 POSTER

Hodgkin's disease in the elderly – Less may be more

D. Feltl, J. Zámečník, P. Vítek. *Institute of Radiation Oncology, Prague, Czech Republic*

Introduction: Patients with Hodgkin's disease (HD) older than 60 years have been treated at our institute with less aggressive approach in effort to minimise the side effects of chemotherapy and radiotherapy. The aim of the study was to compare our results with the data referred elsewhere and to establish the prognostic value of assessed factors.

Methods: From 1973 to 1993 there were 52 elderly (older than 60 years) patients with HD treated following Prague Cooperative Group protocol, which includes a relatively mild chemotherapy regimen (COPP) and/or limited field radiation techniques. Clinical stage, histological subtype, treatment modality, accomplishment of treatment, response to treatment, disease free survival (DFS), overall survival (OS) and tolerance of treatment were assessed using a retrospective analysis.

Results: Of the eligible 52 patients 30 (57.5%) achieved complete remission, 19 (36.5%) partial remission and 3 (6%) had a progressive disease during the treatment course. 5 year disease free survival was 48%. There were 2 independent prognostic factors for DFS and OS: Clinical stage (I, II vers. III, IV) ($p = 0.005$ and $p = 0.007$) and accomplishment of treatment ($p = 0.014$ and $p = 0.011$). There was no prognostic value of histological subtype. A marginally significant difference in DFS and OS is apparent between chemotherapy only (CT) and combined modality treatment (CMT) groups ($p = 0.005$ and $p = 0.06$). No significant difference was found between CT and radiotherapy only (RT) or CMT and RT treatment groups. However there is little covariation of clinical stage between CT or CMT and RT groups. The treatment was in general well tolerated with a very low rate of severe complications and no treatment related death.

Conclusions:

(1) With our less aggressive approach we achieved results comparable to those found in the literature while the tolerance of treatment was better compared to the studies employing more aggressive regimens.
(2) Our results indicate that less aggressive CHT approach may be compensated by addition of RT in favour of compliance in elderly patients with HD.

1341 POSTER

Bcl-6 gene alterations in non-Hodgkin's lymphomas

P.M. Chen, Y.C. Lin, C.J. Chu, F.S. Fan, T.J. Chiou, J.H. Liu. *Section of Medical Oncology, Veterans General Hospital-Taipei and National Yang-Ming University, Taipei, Taiwan, China*

Purpose: In the Western, rearrangements and point mutation (PM) of Bcl-6 gone can be identified in 20–40% and 70% of diffuse large-cell lymphomas (DLCLs). However, there are few reports concerning Bcl-6 gene alterations in Chinese non-Hodgkin's lymphoma (NHL) patients.

Methods: Lymph node samples obtained from 155 patients with NHLs (70 patients with DLCLs) were examined for the presence of gene rearrangements (GR) and PM in the Bcl-6 proto-oncogene using Southern blot analysis and single-strand conformation polymorphism followed by sequence analysis, the histopathologic classification with clinical outcome was then assessed.

Results: GR and PM in 155 NHL patients were 16.7% (n = 25) and 29.7% (n = 46) respectively. Meanwhile, in 70 DLCLs, Bcl-6 GR were identified in 13 (18.6%) and PM in 27 (38.6%). Bcl-6 PM occurred independently of Bcl-6 GR. All of Bcl-6 GR in NHLs were of the B-cell type, whereas 3 PM were derived from the T-cell lineage including a case of adult T-cell lymphoma. By Cox's proportional hazard model for risk factor, these two types of gene alterations in DLCLs or in all NHLs were not associated exclusively with extranodal sites and were not a prognostic predict.

Conclusion: The incidence of Bcl-6 alterations in DLCLs is lower in Taiwan than of in the Western. Clinically, these two types of gene alterations in DLCLs or in all NHLs did not appear to carry any prognostic significance.

1342 POSTER

Increase of the myelodisplastic syndrome (MDS) incedence in Chernobyl-contaminated regions of Belarus can be the first evidence of radiation-dependent leukaemogenesis

V.E. Ivanov, G.V. Tolochko, L.P. Shuvaeva, E.P. Ivanov. *Institute of Haematology and Blood Transfusion, Minsk, Belarus*

In 1986–1992 Belarussian National Registry of Blood Disorders was created in our Institute. It covers 7 years before Chernobyl and all post Chernobyl period. During this years all cases of leukaemia and MDS were collected and analysed, and only from 1996 we were able to establish some disturbances, that seems to be radiation-dependent.

In the years 1996–1997 the increase of MDS among adults, who lives on the Chernobyl-contaminated territories of Belarus, has been found. The incidence for whole Belarus in 1996–1997 was 0.9 per 100.000 population and in contaminated Mogilev region it was 1.32 in 1996 and 3.04 per 100.000 population in 1997. The same picture was evidenced in other contaminated Gomel region: 1.53 in 1996 and 1.05 per 100.000 population in 1997. The FAB classification was introduced in Belarus since 1990 in