of MOPP, a regimen that is typically poorly tolerated, or an inherent difference in response to chemotherapy between patients with relapsed disease and those with newly-diagnosed disease. Nearly one-quarter of the study population developed a second malignancy, likely a reflection of the cumulative treatment exposure.

1012 POSTER

Prediction of severe neutropenia in elderly patients with aggressive lymphoma treated by an anthracycline containing regimen

C. Dagada[1], P. Soubeyran[1], K. Hembert[1], A. Monnereau[1], H. Eghbali[1], J. Ceccaldi[2], P. Guichard[3], O. Hallé[4], P. Rémuzon[5], H. Demeaux[6]. *[1] Institut Bergonié, Regional Cancer Center, Department of Medicine, Bordeaux Cedex, France; [2] Centre Hospitalier, Libourne, France; [3] Polyclinique Bordeaux Nord, Bordeaux, France; [4] Centre Hospitalier, Villeneuve-sur-Lot, France; [5] Centre Hospitalier, Dax, France; [6] Hôpital Saint-André, Bordeaux, France*

Aggressive lymphomas can be cured by an anthracycline-containing chemotherapy, i.e. CHOP or CHOP-like combinations. Althoug very well tolerated in younger patients, these regimens are often associated with high toxic death rate in the elderly, up to 10-15% in some series. Since hematological toxicity appears to be the most important life-threatening toxicity in these patients, it may be worthwhile to search for predicting factors that can allow physicians to either reduce doses or prescribe growth factors in selected cases.

Material and methods: In a search for better management of patients with aggressive lymphomas, older than 65 years and able to receive an anthracycline-containing chemotherapy, a phase II trial of the CEVOP combination (cyclophosphamide: 750mg/m^2 IV d, 4epidoxorubicin: 60mg/m^2 d, etposide: 50mg/m^2 orally d to d, vincristine: 1.4mg/m^2 d, prednisone: 40mg/m^2 orally d to d q3w × 6) has been performed. Hematopoietic growth factors were not proposed routinely. Systematic blood cell counts were performed at 3-day intervals to monitor for hematological toxicity. Among 66 patients included, 55 were available for the current study (209 cycles of chemotherapy). Grade 4 neutropenia (G4N) occurred in 50 cycles (24%). Potential predictive factors including age, performance status (PS), comorbidity, creatinine clearance, bone marrow involvement, day-5 and -8 lymphocyte (d5L,d8L) and monocyte (d5M,D8M) counts were tested for G4N risk.

Results : After univariate analysis, two multivariate analyses have been performed. The first one include PS, d5L and d5M: only PS appeared significantly correlated with G4N occurrence (RR=4.18 - p=.002), d5L having borderline significance (p=.054). The second model included PS, d8L and d8M. Both PS (RR=4.44 p=.014) and d8M (RR=4.18 p=.002) appeared significant while d8L had borderline significance (p=.056).

Conclusion: Overall, these data show that PS, monocyte and possibly lymphocyte counts at day 8 can prédict for grade 4 neutropenia risk. These results may help physician to select elderly patients who might benefit from either use of hematopoietic growth factors or chemotherapy dose reduction.

1013 POSTER

Pharmacokinetic parameters of methotrexate as predictors of toxicity, activity and efficacy in patients with primary central nervous system lymphoma (PCNSL)

A.J.M. Ferreri[1], E. Guerra[2], M. Regazzi[3], F. Pasini[4], A. Gubkin[5], A. Calderoni[6], M. Spina[7], A. Brandes[8], S. Dell'Oro[1], M. Reni[1]. *[1] Dept. of Radiochemotherapy, [2] Laboratorio di Standardizzazione per la Chimica Clinica, Milan, San Raffaele H Scientific Institute, Italy; [3] I.R.C.C.S. Policlinico San Matteo, Dept. of Pharmacology, Pavia, Italy; [4] Ospedale Civile Maggiore, Divisione Clinicizzata di Oncologia Medica, Verona, Italy; [5] Hematological Center of Russian Academy of Medical Sciences, Hematology and Intensive Care Dept., Moscow, Russia; [6] Institut für Medizinische Onkologie Inselspital, Bern, Switzerland; [7] Centro di Riferimento Oncologico, Divisione di Oncologia Medica "A", Aviano, Italy; [8] Azienda Ospedale-Università, Dept. of Medical Oncology, Padua, Italy*

Background: High-dose methotrexate (HD-MTX; ≥1 g/m^2) is the most effective drug against PCNSL. However, its optimal administration schedule and the relevance of its pharmacokinetic parameters have not been defined in PCNSL.

Aim: To define the impact on toxicity and outcome of plasmatic creatinine clearance (CL_{crea}) and the area under the curve (AUC_{MTX}), dose intensity (DI_{MTX}) and infusion rate (IR_{MTX}) of MTX in 75 immunocompetent pts with PCNSL treated with HD-MTX-based chemotherapy (CHT; 1995-2001). The role of anticonvulsant therapy was also analyzed.

Methods: Our series showed the usual clinico-pathological characteristics of PCNSL pts. Treatment consisted of 3 courses of HD-MTX (1-8 g/m^2; every 3 or 4 weeks), alone (n=10) or associated with HD-cytarabine (n=41) or alkylating agents (n=24); followed by whole-brain irradiation (mean tumor dose 45±9 Gy). Anticonvulsants were administered in 46 pts (61%). The individual AUC_{MTX} was determined by two different methods considering MTX dosage, MTX serum levels at 0, 24, 48, and 72 hours after drug infusion and CL_{MTX} (CL_{MTX}= 1,6. CL_{crea}), with mean values of 732±526 and 991±826 μM/L.h (linear regression; p=0.00001), respectively. The cut-offs for analysis were: 85 mL/min for CL_{crea} (slow vs. fast), 650 mg/m^2/h for AUC_{MTX} (low vs. high), 750 mg/m^2/wk for DI_{MTX} (Hryniuk method; upheld vs. reduced), and 1100 mg/m^2/h for IR_{MTX} (administered dose/hour; slow vs. fast).

Results: Fast CL_{crea}, slow IR_{MTX}, reduced DI_{MTX}, and anticonvulsant therapy were significantly correlated to low AUC_{MTX} values (logistic regression). Severe toxicity (CHT interruption or toxic death) was observed in 13 cases; a fast IR_{MTX} was associated with higher toxicity.

Response after CHT was complete in 34 pts (CRR= 45%) and partial in 23 (ORR= 76%); a slow CL_{crea} was independently associated with higher CRR. Thirty-seven pts experienced failure, with a 3-yr FFS of 36±7%; 42 pts were alive (median f-up 20 months, range 3-63) with a 3-yr OS of 40± 8%. Log-rank tests showed a significantly positive impact on survival of slow CL_{crea} (3-yr OS: 71± 12% vs. 31±9%, p=0.02), high AUC_{MTX} (3-yr OS 50± 9% vs. 22±12%, p=0.05) and upheld DI_{MTX} (3-yr OS: 56± 10% vs. 29±10%, p=0.05); while anticonvulsant therapy, IR_{MTX} and CHT regimen were not associated with survival. Cox analysis confirmed the independent prognostic role of age, PS, CL_{crea}, AUC_{MTX}, and DI_{MTX}.

Conclusions: Slow CL_{crea}, high AUC_{MTX} and upheld DI_{MTX} are independently associated with better outcome in PCNSL pts; while fast IR_{MTX} is significantly related to higher toxicity. These findings seem to support the choice of a MTX dose ≥3 g/m^2 administered in a 4- or 6-hour infusion, every 3-4 weeks, in clinical practice, and deserve to be assessed in future trials. MTX dose adjustments to ensure adequate exposure, such as a higher AUC_{MTX}, in pts with fast CL_{crea} or treated with anticonvulsants should be critically considered.

1014 POSTER

Activation antigen (HLA-DR, CD38, CD23) expression by non-neoplastic background cells in Hodgkin's lymphoma (HL)

G. Tumian. *Cancer Research Centre, Haematology, Moscow, Russian Federation*

The objective of the study was to investigate frequency of expression the activation antigens (HLA-DR, CD38, CD23) by non-neoplastic background cells.

Material and methods: We have studied a series of 200 patients with classical HL (cHL) followed at the hematology department beetween 1995-2001. There were 93 (46%) males and 107 (54%) females with a median ages of 29 (range 14-71). As regards histologic type, 2,5% had lymphocyte rich (LRcLH), 50% nodular sclerosis (NScHL), 30% mixed cellularity (MCcHL), 9,5% lymphocyte depletion (LDcHL) and 8% unclassified HL.

Results: The analysis of CD23 has demonstrated that the reactive lymphoid cells of most cases (88%) were CD23-negative and only in 12% of HL cases CD23+ reactive cells were identified. HLA-DR antigens were expressed in 67% cases, in 15% reactions were weak and in 18% - inflamatory cells were HLA-DR negatives. Background non-neoplastic lymphocytes expressed CD38 in 58% cases and were negative in 42% HL. HLA-DR and CD38 antigens expression levels depended on histologic types of HL (table).

Histotypes	HLA-DR+	CD38+
LRcHL	50%	80%
NScHL	64%	55%
MCcHL	82%	72%
LDcHL	45%	35%

Conclusions: Immunophenotypic studies have confirmed that antigen profile of non-neoplastic cells was different and correlate with histologic types of HL. The functional relationship between the neoplastic Hodgkin's and Reed-Sternberg cells and the inflammatory background infiltrate is not understood fully and should be futher investigated.