In-field failures were registered after standard 40 Gy in 13.7% (7/51 patients, 95% confidence interval (CI): 4.2% to 23.1%) and after 24 Gy AHFX in 10.7% (7/66 patients, CI: 3.2% to 18.0%). Median time to in-field-failure was shorter in chemoresistant relapse: 4 months (range 1-11) versus 15 months (range 8-21) in chemosensitive relapse and refractory patients altogether. Out-of-field progression occurred in 51% (27/53 patients) and 28% (11/39 patients) cases, respectively. Median time to out-of-field progression was 4 months (range1-27) and 15 months (8-24), respectively. Deaths from progressive disease occurred in 10 relapsed patients; 2 patients died of treatment-related AML and AMML.

Conclusions: This randomized study suggests that the low-dose RT in AHFX regimen can provide the similar rate and duration of local control for post-CT residual disease as standard 40 Gy.

1009 POSTER

Phase II clinical experience with the novel proteasome inhibitor bortezomib (formerly PS-341) in patients with indolent and mantle cell lymphomas

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The ubiquitin proteasome pathway plays an essential role in the degradation of most short- and long lived intracellular proteins in eukaryotic cells. At the heart of this degradative pathway is the 26S proteasome, an ATP dependent, multicatalytic protease. The 26S proteasome plays a vital role is degrading regulatory proteins that govern cell cycle, transcription factor activation, apoptosis and cell trafficking. Some of the targets of ubiquitin proteasome mediated degradation include p53, p21, NF-κ B, Iκ B and *bcl*-2. Several lines of preclinical data have confirmed that inhibitors of the proteasome can act through multiple mechanisms to arrest tumor growth, tumor spread and angiogenesis. Phase I trials have confirmed tolerability of the drug and have suggested possible clinical activity in indolent lymphomas and myeloma. Correlative studies performed in the Phase I and II clinical trials have established a dose response relationship between dose and the extent of proteasome inhibition seen in peripheral blood mononuclear cells. To date, we have administered over 65 cycles of PS-341 (average 3.8 per patient) to 17 previously treated patients with relapsed or refractory indolent lymphomas (small lymphocytic lymphoma-CLL type (n=2); marginal zone lymphoma (n=1); follicular lymphoma (n=7) and mantle cell lymphoma (n=7). All patients were required to sign and informed consent and had to have adequate hepatic and renal function. Adequate hematologic counts including an ANC of > 1000 cells/μ l and a platelet count > 100,000/μ l were also required. All patients had received some form of treatment prior to receiving PS-341, including: CHOP; CVP; cyclophosphamide/fludarabine; rituximab; interferon, and one patient who had received two regimens of a complex combination chemotherapy program that included alkylating agents, tubulin inhibitors, anthracyclines and antimetabolites. Patients were treated at a dose of 1.5 mg/m2 twice weekly for two consecutive weeks with a one week rest period. Re-staging studies were routinely performed after two complete cycles of therapy. Both patients with small lymphocytic lymphoma were found to have stable disease after 2 and 4 cycles respectively. Of the 6 evaluable patients with follicular lymphoma, there was one CR, 5 PR (i.e > 50% reduction in tumor volume). Of 7 patients with mantle cell lymphoma (1 not evaluable for response yet), 3 patients had a PR, 3 had stable disease. One patient with MCL continues to maintain his PR (> 80% reduction in his disease) at 14 months since the completion of therapy. These preliminary data continue to support the biological activity of PS-341 in patients with indolent lymphomas, especially follicular and mantle cell lymphoma. Accrual to this trial continues.

1010 POSTER

Hairy cell leukemia: early immunological diagnosis and quantitative analysis of flow cytometry

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(1) Background. Immunophenotypic analysis of bone marrow (BM) and peripheral blood (PB) by flow cytometry is not widely used as a method for diagnosis HCL. The abnormal coexpression of the so-called 'HCL-restricted' markers - CD22+CD11c, CD25 and CD103 on monotypic, slightly large B-lymphocytes has been shown to be highly characteristic of HCL. The main aim of our study was to determine if patterns with low levels of neoplastic cells in BM or PB are valuable in the diagnosis and minimal residual disease (MRD) detection in HCL. Next we wished to determine if quantitative immunophenotyping given by molecules of equivalent soluble fluoresceine (MESF) could help to distinguish pathological B-lymphocytic pool. We investigated serially lymphocyte subsets after treatment with 2-Chlorodeoxyadenosine (CdA) to confirm CD4+ lymphopenia. (2) Material and methods. The abnormal immunophenotypes were studied in 18 patients with suspect HCL (all patients had other manifestations of HCL), or during follow-up of already treated patients. Flow cytometric measurement was performed on an EPICS ALTRA Flow Cytometer using double- or triple-staining and Expo 32 program for analysis. For evaluation of marker density expressed in flow cytometry by mean of fluorescence intensity, fluorescent calibration microbeads were used. (3) Results. In 12 HCL patients (67%) permanent complete remission was observed after treatment. In the rest of 6 patients (33%) we identified transient MRD+ phenotype but the clinical manifestation of relapse was followed in only three patients. The pathological cells in low levels were found in 4 patients at diagnosis (in the range of 7 to 18%) and in patients with MRD+ phenotype they were recognized repeatedly in the range of 2 to 8%. Furthermore, we observed in hairy cells significantly higher values of molecule numbers of B-cell markers, comparing to residual B-cells in nonleukemic lymphocyte gate of the same sample. We found profound and persistent CD4+ lymphopenia in majority of studied patients after CdA treatment. (4) Conclusions. Flow cytometric immunophenotyping is highly sensitive and specific method and is capable to detect low levels of malignant cells in HCL. Quantitative analysis of MESF values of pathological and normal residual B-cells seems to be a new marker of HCL, reliable detecting also small cell numbers in examined sample. A long-term decline of CD4+ T-cells correlated with the relatively low incidence of clinical progression of HCL.

1011 POSTER

Comparison of MOPP versus ABVD as Salvage Therapy in Patients Who Relapsed After Radiation Therapy Alone for Hodgkin's Disease

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Purpose: Randomized trials by cooperative groups have demonstrated the superiority of Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) over mechlorethamine, Oncovin, procarbazine, prednisone (MOPP) in the treatment of newly-diagnosed Hodgkin's disease (HD). We sought to compare the efficacy of the 2 regimens as salvage therapy in patients with relapsed HD after radiation therapy (RT) alone.

Methods: 100 patients with HD initially treated with RT alone between 1980 and 1997 subsequently experienced a relapse. 41 patients were salvaged with MOPP and 59 received an ABVD-containing regimen. Freedom from second relapse (FSR), defined as time from the end of salvage treatment to second relapse, death or end of follow-up, and overall survival (OS), defined as time from the end of initial treatment to death or end of follow-up, were estimated using the Kaplan-Meier method. Survival curves were compared using log-rank tests. Cox proportional regression models were used to evaluate potential predictive factors. Variables analyzed were: age at diagnosis, histology, number of initial sites, time to first relapse, relapse stage, extranodal disease at relapse and salvage chemotherapy regimen.

Results: The median follow-up time after first relapse was 12 years for all patients (range, 1-22 years), 17.3 years for MOPP patients (range, 7-22 years) and 8.3 years for ABVD patients (range, 1- 18 years). The 10-year FSR rates for all patients, MOPP patients and ABVD patients were 70%, 72% and 68%, respectively (MOPP vs. ABVD: p=0.62). The corresponding 10-year OS rates were 89%, 85% and 92%, respectively (MOPP vs. ABVD: p=0.64). On univariate analysis, age ≥50 at initial diagnosis significantly predicted for lower FSR (p=0.001) and OS (p=0.0001). On multivariate analysis, age ≥50 significantly predicted for inferior FSR [hazards ratio (HR)=9.1, p=0.0001] and OS (HR=8.5, p=0.001). No other factors were significant. Of the 41 MOPP patients, 12 (29.3%) developed a second malignancy (2 leukemia, 1 non-Hodgkin's lymphoma and 9 solid tumors). Of the 59 ABVD patients, 11 (18.6%) developed a second malignancy (1 leukemia, 2 non-Hodgkin's lymphoma and 8 solid tumors).

Conclusions: Patients who relapse after RT alone for HD have a high salvage rate. Older age at diagnosis is the only significant predictor for poorer salvage outcome. In contrast to initial HD therapy, MOPP and ABVD showed no significant differences in efficacy as salvage therapy for RT failure. Potential explanations for the lack of differences could be a greater likelihood in a single-institutional setting to push for full doses

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

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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)

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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)

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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.