by the release of nuclear mitotic apparatus protein and by the translocation of phosphatidylserine at the cell surface. Differention of cells was monitored by flow cytometry using FITC- or PE- conjugated monoclonal antibodies against CD14, CD41a and Rh D antigens. Hemoglobin synthesis was measured by benzidine/peroxide staining.

Results: BT 99-25 and BT 99-45 caused a dose-dependent inhibition of proliferation of K562 cells without inducing apoptosis. Rather, the cellular division arrest was associated with a significant differentiation of K562 cells into megakaryocyte-like, monocyte-like or erythrocyte-like cells in a dose-dependent manner. At 100 μg/ml, BT 99-25 upregulated the expression of CD14, a marker of monocyte differentiation, CD41a, a marker of megakaryocyte differentiation, and Rh D, a marker of erythrocyte differentiation by 9.8, 18.9 and 15.4 fold respectively over control while BT 99-45 upregulated the expression of CD14, CD41a and RhD by 3.7, 11.7 and 4.7 fold respectively over control. In addition, we found that BT 99-25 and BT 99-45 were able to induce hemoglobin synthesis by K562 cells and to increase their cell volume, two measures of erythroid differentiation. In the presence of 100 μg/ml of BT 99-25, 35.8% of K562 cells synthesized hemoglobin and in the presence of 100 μg/ml of BT 99-45, 11.4% produced hemoglobin. Only 5.4% of untreated K562 cells produced hemoglobin in this assay system.

Conclusion: Our data show that BT 99-25 and BT 99-45, two synthetic 6 base length phosphodiester oligonucleotides, possess the ability to induce the differentiation of K562 cells. These oligonucleotides may have potential as differentiating agents in CML therapy.

71 POSTER DISCUSSION

Pilot trial of infusional cyclophosphamide, doxorubicin, and etoposide (CDE) plus the anti-CD20 monoclonal antibody (rituximab) in HIV-associated non-Hodgkin's lymphoma (NHL). Preliminary results of an international multicentre trial

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Recent data suggested that the combination of rituximab plus CT is more effective in the treatment of high grade NHL. With the aim to evaluate the efficacy and activity of combining infusional CDE plus rituximab, in June 1998 we started a phase II study using infusional CDE (cyclophosphamide 200 mg/mq/day, doxorubicin 12.5 mg/mq/day, and etoposide 60 mg/mq/day) given by continuous intravenous infusion for 4 days every 4 weeks for up to 6 cycles plus rituximab (375 mg/mq) by one of two schedules: prior to each cycle of CDE (25 patients-pts) or on day-8 and day-1 prior to cycle 1, just prior to cycles 3 and 5, then on days 28 and 35 after the last cycle (5 pts). From June 1998 to October 2000, 30 pts have been enrolled and 29 pts are evaluable for response and toxicity. Twenty-four (83%) pts are male and the median age was 28 yrs (range 29-65). The median CD4 count was 132/mmc (range 3-470) and the median PS was 1 (range 0-3). Fifty-five percent of pts had stage III-IV disease and 55% had B-symptoms. Twenty-four out of 29 pts (83%) achieved CR, 1/29 (3%) had partial remission and 3 pts (10%) progressed. Only 1 pt out of 24 CRs (4%) have relapsed. Grade III-IV neutropenia was observed in 79% of pts, anemia in 45% of pts and thrombocitopenia in 34% of pts. Thirty-four percent of pts developed bacterial infections during neutropenia. No toxic deaths were observed. With a median follow-up of 9 mos, the actuarial overall survival and progression free survival at 2 yrs were 80% and 79% respectively. The combination of rituximab plus infusional CDE in pts with HIV-associated NHL is safe and feasible with an increase of bacterial infection. However, all infections were cured with antibiotics and no toxic deaths were observed. Further study of this combination is warranted. Supported by AIRC and ISS grants.

72 POSTER DISCUSSION

IELSG prognostic score for primary central nervous system lymphomas (PCNSL): analysis of an international series of 378 immunocompetent patients

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Purpose: Reliable prognostic factors in PCNSL, apart from age and PS, have not been consistently defined. An international series of 378 immunocompetent patients was reviewed to identify survival predictors and to design a prognostic score useful to distinguishing risk groups.

Methods: Median age was 61 ys (12-85); ECOG-PS >1= 222 (65%). High LDH serum level in 69/195 (36%), ocular involvement in 22/170 (13%), meningeal spread in 38/241 (16%), elevated CSF protein concentration in 82/134 (61%), involvement of deep structures of the brain (periventricular regions, basal ganglia, stem brain, and/or cerebellum) in 136 (36%) cases. Treatment was chemotherapy (CHT) in 32 (8%) cases, radiotherapy (RT) in 98 (26%), RT-CHT in 36 (9%), CHT-RT in 197 (53%), none in 7 (2%), data were not available in 8 (2%).

Results: Age <60 ys (2-yr OS: 46±3% vs. 29±3%, log-rank test, p=0.00006), PS <2 (50±5% vs. 31±3%; p=0.00001), normal LDH serum level (49±4% vs. 29±5%; p=0.008), normal CSF protein level (61±7% vs. 39±5%; p=0.003), and absence of involvement of deep regions of the brain (42±3% vs. 28±4%; p=0.0006) were significantly and independently (Cox analysis) associated with a better outcome. These 5 variables were used to design a prognostic score, considering '0' the favorable feature and '1'the unfavorable one and summing the 5 results. This score was tested in 105 assessable patients for whom complete data of all the 5 variables were available. The 2-yr OS was 80±8%, 48±7% and 15±7% (p=0.00001), respectively for patients with 0-1, 2-3 and 4-5 unfavorable features. This prognostic score was tested separately on the subset of 75 assessable patients treated with HD-MTX-based CHT±RT achieving similar results, with a 2-yr OS of 85±8%, 57±8% and 24±11% (p=0.0004), respectively for patients with 0-1, 2-3 and 4-5 unfavorable features.

Conclusions: Age, PS, LDH serum level, CSF protein concentration, and involvement of deep structures of the brain were independent predictors of survival. The combined analysis of these 5 variables resulted in a prognostic score useful to distinguishing different risk groups, even in patients treated with HD-MTX-based CHT±RT. The independent role of these 5 variables and the clinical relevance of the proposed prognostic score deserve to be assessed in further studies. This score could become useful in stratifying patients and comparing results in future prospective trials.

Central nervous system tumours

73 POSTER DISCUSSION

IMT-SPECT in gliomas: correlation with survival and consequences for target volume definition

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Purpose: 1) To evaluate the prognostic value of IMT-SPECT (Iodine-123-alpha-methyl-tyrosine single photon emission computed tomography) in patients with brain gliomas treated with radiation therapy.

Materials and Methods: In 121 patients (76 resected and 45 non-resected) with brain gliomas the IMT-SPECT investigation was co-registrated with the MRI data and the fusion images were integrated in the 3D radiation treatment planning. The accuracy of the overlay images has been previously analyzed in phantom studies and in patients. The reproducibility of the reorientation is approximately 2 degrees for rotation and 3 mm for translation. IMT-uptake at the site of the tumor was assessed visually and quantified relative to a contralateral reference region (IMT uptake ratio). Tumor borders in IMT-SPECT were obtained automatically, using a threshold-technique. A second IMT-SPECT/MRI investigation at 40 Gy (total dose 60 Gy) quantified the IMT uptake during radiotherapy.

Results: In the group of resected patients the IMT was visible in 52 of 76 cases (73%). The intensity of IMT uptake significantly correlated with survival: patients with an IMT uptake ratio of more than 1.7 were at a 4.6 times higher risk of death compared to patients with lower IMT uptake ($p < 0.001$). The IMT uptake ratio remained a significant prognostic factor when age and grading were included in a multivariate model. In contrast, IMT uptake did not correlate with survival in previously unresected patients ($p = 0.95$). The reduction of the IMT uptake under radiation therapy (by 40 Gy) was significant both in the resected (p=0.007) and in the non-resected group (p=0.016).

Conclusion: The clear association between focal IMT uptake after tumor resection and poor survival suggests that IMT is a specific marker for residual tumor tissue. The IMT uptake decreases under radiation therapy. IMT-SPECT is a valuable tool for the radiation treatment planning, especially for the definition of the target volume for dose escalation.