Conclusion: This study demonstrates promising activity and good tolerability of ALIMTA in mesothelioma. Randomized trials that will further define the role of ALIMTA in this disease are ongoing.

67 POSTER DISCUSSION

Gemcitabine plus Carboplatin (Gcarb) versus Cisplatin plus Vinblastine (CV) in Patients (pts) with Stage IIIB and IV Non-Small Cell Lung Cancer (NSCLC)

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Purpose: The combination of Gcarb has demonstrated activity in the treatment of stage III and IV NSCLC. This phase II randomized trial compared the response rate, survival rate, and toxicity of the combination of Gcarb with the combination of CV.

Methods: Chemonaive patients with advanced or metastatic NSCLC were enrolled in the study. Pts were randomized to receive either cisplatin 75 mg/m2 on day 1 plus vinblastine 6 mg/m2 on days 1 and 8 (arm A) or gemcitabine 1000 mg/m2 on days 1 and 8 plus carboplatin 300 mg/m2 on day 1 (arm B). Both regimens were administered on a 21-day course.

Results: A total of 198 patients (99 pts each in arms A and B) were enrolled in the study between July 1997 to November 1999. All pts had an ECOG performance status <2. Patients had a median age of 58.2 years (range, 30 to 78) in arm A and 59.6 years (range, 40 to 78) in arm B. In arm A, there were 15 partial responders (PR), for an overall response rate (ORR) of 15%, compared with 3 complete responders (CR) and 24 PR, for an ORR of 27% ($p < 0.05$), in arm B. Mean survival times were 239 days (95% CI, 214 - 265) in arm A and 349 days (95% CI, 299 ± 390) in arm B. One-year survival rates for arms A and B, respectively, were 9.1% and 20.2%. Percentages of pts with WHO grade (G) 3/4 hematologic and non-hematologic toxicity in arms A/B were leukopenia 0/2, thrombocytopenia 0/2, alopecia 46/33, neurotoxicity 2/1, and asthenia 35/42.

Conclusion: The Gcarb combination showed a good therapeutic response, a benefit in survival, and a similar toxicity profile compared with the CV combination.

Hematological malignancies

68 POSTER DISCUSSION

An allogeneic antitumor effect after hematopoietic stem cell transplantation for colorectal and renal carcinoma

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Purpose: Does allogeneic hematopoietic stem cell transplantation (ASCT) have an anticancer effect in colorectal and renal carcinoma?

Methods: Five patients with colorectal and nine patients with renal adenocarcinoma with metastases underwent ASCT. The donors were HLA-identical siblings for nine patients and HLA-compatible unrelated donors for five patients. Conditioning included Fludarabin 30 mg/m2 for three days in patients with HLA-identical siblings and five days with unrelated donor, followed by 2 Gy total body irradiation. Antithymocyte globulin 4 mg/kg was given to patients with unrelated donors. Peripheral blood stem cells were collected after G-CSF stimulation of all donors. Immunosuppression was by mucophenolate mofetil and cyclosporine. Chimerism was determined using PCR amplification of variable number tandem repeats.

Results: All patients were treated as outpatients. Chimerism showed 100% donor myeloid and T-cells in 7/14 and 2/14 patients at one month after ASCT, respectively. Six patients developed grades II-IV acute GVHD. Two rejected the grafts, one died of renal toxicity, one died of an accident and two died of disease progression. One patient with colon cancer showed an 80% decrease in size of all metastases at two months. He died of pneumonia at four months and autopsy showed necrosis of all metastases with few cancer cells. Another patient with colon carcinoma have shown regression of pleura metastases, but progression of liver metastases. One patient with renal carcinoma died of grade IV acute GVHD. Pulmonary metastases had disappeared at autopsy. Among four renal carcinoma patients who are alive between 4 and 12 months after ASCT, one has shown partial response of metastases, another has shown progression as well as regression of metastases.

Conclusion: ASCT after minimal conditioning was well tolerated. 7/14 patients are alive after 4-12 months. Partial tumor regression (>50%) was seen in two patients with colorectal and two patients with renal carcinoma.

69 POSTER DISCUSSION

High activity rhenium-186 HEDP with peripheral blood stem cell support -a novel approach to hormone refractory prostate cancer metastatic to bone

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Purpose: The radioisotope Rhenium-186 HEDP has been used successfully for many years in the palliation of pain from bone metastases, with thrombocytopenia as the dose limiting toxicity. In this study we have tested the feasibility of escalating activities of Rhenium-186 HEDP by using peripheral blood stem cell support in a phase I trial. We hypothesise that by increasing the administered activity it will be possible to increase the ionising radiation dose to individual metastases allowing potential ablation of small lesions, reduction in new lesion formation, and improved disease free survival.

Methods: Twenty patients with hormone refractory prostate cancer metastatic to bone, minimal soft tissue metastases, and rising PSA, each received one treatment of intra-venous Rhenium-186 HEDP. Stem cells were returned 14 days post isotope treatment. A starting activity of 2500MBq was chosen following previous work by ourselves showing unacceptable toxicity without stem cell support at 3000MBq. We have now reached activities of 5000MBq, initially with increments of 250MBq and subsequently 500MBq when low toxicity rates were seen.

Results: All patients tolerated the treatment and stem cell transplant well. There was no incidence of grade III platelet toxicity (<50 x 109/l). Three patients (15%) had grade III leucopenia (1-2 x 109/l). A trend towards lower nadir platelet levels was seen with activities of Rhenium-186 above 3500MBq (p=0.1). Each patient had a total of 4 days spent in hospital for radioprotection purposes with all other procedures performed on an outpatient basis. As yet we have not found the maximum tolerated activity. Actuarial survival figures are encouraging compared to the literature with a median survival of 9.8 months at a median follow up of 7.5 months (range 2-36). PSA responses were seen in 60% of patients with a non statistically significant trend towards better response above 3500MBq (p=0.37).

Conclusions: Activities up to 5000MBq of Rhenium-186 HEDP can be administered with peripheral blood stem cell support with minimal toxicity. The potential exists for higher doses of ionising radiation to be delivered to individual metastases. We plan to continue phase I until the maximum tolerated activity is reached and then proceed to a Phase II evaluation of response.

70 POSTER DISCUSSION

Induction of differentiation of human chronic myeloid leukemia cells by synthetic 6 base phosphodiester oligonucleotides

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Purpose: A series of synthetic 6 base non-antisense phosphodiester oligonucleotides with either GpA, GpC, GpG or GpT dinucleotides motifs within specific sequence contexts has been identified as a potent inducer of apoptosis in a wide range of cancer cells, including acute lymphocytic leukemia cells. In this study, we have evaluated the activity of these oligonucleotides on a human chronic myeloid leukemia (CML) cell line.

Methods: K562 cells, derived from the leukemic cells of a CML patient in blastic crisis, were incubated for 48 h with different concentrations (2.5 to 100 μg/ml) of oligonucleotides with either GpA (BT 99-45) or GpT (BT 99-25) dinucleotides motifs within specific sequence contexts. Cellular division was monitored using a Coulter Counter. Apoptosis was evaluated

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.