administered at 500 mg (highest safe dose from Part 1) with 5-FU/LV between days 8-12 (cycle I) and days 36-40 (cycle 2). Dose-limiting toxicity (DLT) up to 56 days was defined as the occurrence of drug-related: G3/4 neutrophil or platelet toxicity (>7 days duration); febrile neutropenia; G3/4 skin rash; G3/4 diarrhea, nausea or vomiting (>4 days duration) despite standard supportive measures; significant ocular toxicity; or occurrence of other G3/4 major end organ toxicity. One-hundred and thirty courses have been delivered in Parts 1 (117) and 2 (13), respectively, and DLT has not been observed to date. GI/2 adverse events (AEs) reported included rash, diarrhea, mucositis and neutropenia. G3/4 AEs included neutropenia and G3 diarrhea in 1 pt. No apparent increased frequency or severity of diarrhea or skin toxicity beyond that seen with 5-FU/LV alone was observed. In addition, there was no evidence of cumulative toxicity or emergence of new or unusual toxicity with continued exposure. No significant drug-drug interactions have been observed following preliminary PK analysis of ZD1839 and 5-FU exposure at 250 mg I-ZD1839. At day 56, after two 5-FU/LV courses and 2 wks ZD1839, I complete and 4 partial responses (3 confirmed) have been observed on the I-ZD1839 schedule. Thus, the combination of ZD1839 and 5-FU/LV is feasible and has a manageable safety profile.

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60 POSTER DISCUSSION

A phase II study of gemcitabine and oxaliplatin (gemox) in advanced billary adenocarcinoma (ABA). Preliminary results

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Pre-clinical data support an optimal synergistic effect using the sequence gemcitabine followed by oxaliplatin (Faivre S, Cancer Chemother Pharmacol 1999, 44(2):117-23). Based on the results of the gemcitabine oxaliplatin combination in advanced pancreatic adenocarcinoma (Louvet C, Proc Am Clin Oncol 2001; 20), we designed a phase II, to determine activity and tolerance of this combination in ABA. Since July 2000, twenty two eligible patients (pts) received the GEMOX regimen: GEMcitabine 1000 mg/m* in 10mg/m*/mn infusion D1, OXaliplatin 100 mg/m* in 2h infusion D2; treatment was repeated every 2 weeks until progression of disease or limiting toxicity. Eligibility criteria were pathologically-proven biliary adenocarcinoma, PS (ECOG) 0-3, age 18 to 80 yrs, adequate hematological, renal and liver functions, measurable disease, control of pain and jaundice before inclusion, and written informed consent. Pts characteristics: 12 male/10 female; mean age 70 yrs, range 40-80; PS: 0 = 7, 1 = 9, 2 = 5, 3 = 1; 2 Locally Advanced (LA)/20 Metastatic (M); chemotherapy line: 1 = 19, 2 = 2, 3 =1; tumor sites: gallbladder 8, extrahepatic bile ducts 3, ampula of vater 3, intrahepatic bile ducts 7, unknown 1; M tumor sites: liver = 16, lung = 3, distant lymph nodes = 2, peritoneum = 4. Toxicity: 139 cycles were administered (median 5, range 1-18). No NCI CTC grade 4 was observed. Grade 3 (% cycle/% of pts): neutropenia 0.7%/4.8%, thrombocytopenia 0.7%/4.8%, nausea-vomiting and diarrhea 0%/0%; grade 2 alopecia 9.5%, grade 3 peripheral neurotoxicity (specific scale) 4.8% of pts. Overall, 14.3% of pts experienced a grade 3 toxicity. Efficacy: (investigators) 5 PR, 3 SD, 6 PD and 8 to early were observed for a response rate (WHO criteria) of 35.7% (5pts/14).

Conclusion: GEMOX combination is active and well tolerated in ABA. Accrual continues to this study. Updated data with progression free survival and overall survival will be presented at the meeting.

61 POSTER DISCUSSION

Partial duodenopancreatectomy with radical lymphadenectomy in patients with pancreatic carcinoma

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Purpose: Partial duodenopancreatectomy (PD) is the treatment of choice for carcinoma of the pancreatic head and periampullary carcinoma. In contrast the benefit of radical lymphadenectomy in these patients is still discussed controversially.

Methods: 117 patients with ductal adenocarcinoma of the pancreas who underwent PD between 1988 and 2000 and received either a regional lymphadenectomy (Group A) or an extended radical lymphadenectomy (Group B) were included in survival studies according to Kaplan-Meier. 52 male and 65 female patients with an median age of 62 years were analysed.

Results: Perioperative mortality was 4.3% (5 pat.). The stage distribution according to the UICC was: Stage I: 8 (6.8%), stage II: 23 (19.7%) stage III: 58 (49.6%), Stage IVa+b: 28 (23.9%). Overall 5-year survival rate of these patient was 18%. 5-year survival of curative (R0) resected patients was 23%.

A significant difference could be observed in these group between patients with negative lymph node status (36% 5-year survival) and positive lymph node status (17% 5-year survival). Whether no significant difference could be observed between patients in Group A or B. If only early UICC-tumor stages were compared patients in Group B seemed to have a benefit in survival compared to group A.

Conclusion: The data indicate that extensive retroperitoneal tissue clearance for ductal adenocarcinoma does not improve overall survival compared to regional lymphadenectomy. Patients with early tumor stages might benefit from the extended approach.

62 POSTER DISCUSSION

Intra-arterial hepatic chemotherapy with oxaliplatin combined to intravenous treatment with 5FU + folinic acid in hepatic metastases of colorectal cancer

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Purpose: Due to increase of tumoural exposure to the drugs, intra-arterial hepatic chemotherapy (IAHC) increases response to chemotherapy when fluoropyrimidines (5FU or FUDR) are used. With new drugs such as oxaliplatin and irinotecan the interest of this sometimes difficult way of therapy has been debated. We tried to use one new drug, oxaliplatin, administered intra-arterially in order to increase response rate and to decrease systemic toxicity.

Methods: From May 1999 to January 2001, 23 patients with isolated hepatic metastases of colorectal cancer were included in a phase II study. Patients could have received one previous treatment combining 5FU + folinic acid for their metastatic disease. They should have adequate bone marrow function and adequate liver, cardiac and renal functions. Study protocol: every two weeks the patients received: oxaliplatin 100 mg/m2 IAH 2-hour infusion + FA 200 mg/m2 2-hour infusion i.v. followed by 5FU 400 mg/m2 i.v. bolus followed by 600 mg/m2 as continuous infusion for 22 hours day 1, FA and 5FU were repeated day 2.

Results: 14 men, 19 women, median age: 59 years [44-72]. The median percent of liver involvement was 30% [10-60%]. Median number of cycles was 6 [1-20]. Treatment was stopped in 15 patients (pts): for progressive disease: 2 pts, obstruction of the catheter: 9 pts, other reason: 4 pts. Toxicity was frequent but mild. Grade 3-4 leucopenia: 4 pts, neutropenia: 7 pts, thrombopenia: 1 pt. There was one toxic death due to a neutropenic sepsis. Response rate in 14 evaluable patients (7 too early, 2 less than 4 cycles due to early catheter obstruction): complete response: 1 pt, partial responses: 10 pts, stable disease: 3 pts; objective response rate: 79%. Three patients underwent complete resection of their metastases after response to IAHC. Six-month survival was 86% [66%-95%].

Conclusion: this combined hepatic arterial with oxaliplatin and systemic chemotherapy allowed to observe very high response rate with manageable toxicity.

Lung cancer 1

63 POSTER DISCUSSION

Randomised phase II study of BMS-275291 versus placebo in patients (pts) with stage IIIb or IV non small cell lung cancer (NSCLC) receiving paclitaxel + carboplatin (PC): National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) br.18

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BMS-275291 is a novel matrix metalloprotease inhibitor (MMPI) with broad activity against MMPs but without the dose limiting arthrotoxicity seen with BB2516 (marimastat) and AG3340 (prinomastat). The objective of the phase II study was to determine the incidence of arthrotoxicity and other toxicities, as well as to examine whether the objective response rate for either arm was in keeping with that expected for PC based upon review

of the literature (~20%). The study would expand to phase III providing that at least 3 responses were seen in the first 30 evaluable patients in the BMS-275291 arm and the one sided lower limit of the 95% CI for grade 2 or worse arthritis, arthralgia and/or myalgia was less than 50%. Eight centres (Canada [4], France [1], Germany [1], Italy [1], Spain [1]), participated in the study. Pts were randomized to BMS-275291at a dose of 1200 mg po bid or placebo, given in combination with 8 cycles of PC [paclitaxel 200mg/m2 and carboplatin AUC 6 q 3 weeks]. After completion of PC, pts continued BMS-275291/placebo until disease progression (PD) or unacceptable toxicity. The endpoints were incidence of grade 2 or worse drug related arthrotoxicity, objective response and toxicity. The planned sample size was 60 response evaluable pts (defined as pts who received 2 cycles of PC and had been reassessed for response; pts who discontinued PC early with PD were also response evaluable). 75 pts were randomized and 65 were response evaluable. Patient characteristics: performance status was ECOG 0/1/2 in 37/54/9%; median age 60 years; 92% of pts were stage IV; 74% were male. The most common sites of disease were regional and other nodes, pleural effusion, bone and adrenals. Toxicity, including hematologic, was that expected for PC, although there was a higher incidence of drug related rash (usually grade 1 or 2) in pts receiving BMS-275291 (26% vs. 11%). Arthrotoxicity was reported in 30-32% in each arm. The objective response rate was > 20% in each arm. We conclude that BMS-275291 was generally well tolerated when given in combination with PC, was not associated with dose limiting arthrotoxicity and did not appear to adversely impact on early tumour shrinkage with PC chemotherapy; as planned, the study has progressed to phase III to examine the impact of BMS-275291, in combination with PC, on overall and progression free survival.

64 POSTER DISCUSSION

Single agent gemzar (G) and taxotere (T) given as 1st/2nd line therapy are active in advanced NSCLC: survival data from two randomized phase II studies

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G and T have been shown to be active in chemotherapy-naive and pre-treated patients (pts) with no cross resistancy. We studied G and T in various doses and schedules giving G or T up to 6 cycles first. The form of drug administration was in the first study IA q4w; G: d1,8,15; 1000mg/sqm followed by IB q4w, D: d1,8,15, 35mg/sqm and vice versa and in the second study IIA q3w; G: d1,8; 1250mg/sqm followed by IIB q3w; D: d1; 100mg/sqm and vice versa again, respectively. In case of tumor progression the opposite drug was used up to 6 additional cycles.

In total 405 pts entered the studies (IIIB/IV 15%/85%; PS<1/>1: 72/28%), and 236 have been analyzed so far. Number of pts in IA/IB/IIA/IIB were 96/48/45/47, the median survival (MS) in months were 8/5/6.5/9.5 with the corresponding confidence intervals in months [5.5;10.5]/[3.0;6.5]/[4.5;8.5]/[7.0;11.5], respectively. 1-year survival in % were 30/19/27/28 and the number of censored observations in % were 15/4/29/30, respectively.

MS differs significantly between IA and IB (Kaplan-Meier [KM]), log-rank [lr] p=.023, rank sum [rs] p=.012), but not between IIA and IIB. So far, IIA and IIB can be considered as equally efficacious, although the MS has been different. IA vs IIA and IA vs IIB showed no difference in KM. IIB is significantly superior to arm IB (lr: p=.0071 and rs: p=.0009). G and T as administered in IA, IIA, and IIB is efficacious and indicates that G and T given as 1st/2nd line treatment approach may be an alternative therapy option to conventional combination chemotherapy.

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65 POSTER DISCUSSION

Detection of occult tumour cells in bone marrow of patients with lung cancer

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Purpose: To develop a reliable assay system for detection of micrometastases in BM in lung cancer patients using immunomagnetic beads coated with monoclonal anti-carcinoma antibodies

Methods: Consecutive patients with inoperable lung cancer admitted to hospital from Jan 2000–April 2001 were sampled. Twenty ml of BM aspirates from the posterior iliac crest were taken from each patient and mononuclear cells were isolated by Lymphoprep (Nycomed, Oslo, Norway) centrifugation and incubated with Dynabeads M-450 (Dynal, Oslo, Norway) coated with MOC 31 and 5T4 antibodies. MOC 31 recognises an epithelial-associated transmembrane glycoprotein often expressed in epithelial tumors.

5T4 is known to bind different types of carcinomas. The cells with iron containing beads bound to their surface were isolated using a strong magnet.

Tumour cells present in the enriched cell fraction were identified in a light microscope as cells with membrane rosettes of at least five beads

Results: At present, 131 BM samples from 111 patients have been examined, includingh 56 adenocarcinomas, 42 squamous carcinoma, and 10 SCLC. In adenocarcinoma patients, 30/56 (53%) BM samples were MOC 31 positive and 17/56 (30%) 5T4 positive. In the squamous carcinomas group, 17/42 (40%) samples were MOC 31 and 27/42 (64%) were 5T4 positive. In SCLC patients, the numbers were 5/10 MOC 31 and 2/10 5T4 positive. In the patients where repeated samples could be drawn, consistent results were obtained.

Conclusions: Immunomagnetic beads coated with MOC 31 and 5T4 antibody detects occult metastases in bone marrow in patients with lung cancer at a very high rate. The method is simple an fast, and the sensitivity is high obtained through the enrichment of the cells to be screened by immunomagnetic selection. The high frequency of positive cases compared to published results with other methods, seems to reflect this advantage. The MOC 31 antibody is superior to 5T4 in detecting adenocarcinoma cells, with an inverse situation in squamous carcinoma, demonstrating an advantage of using both antibodies in parallel. As for other tumour types, micrometastatic cells in BM may be an independent prognostic marker. In operable lung cancer patients, the assay may useful in selecting patients at high risk of relapse and possibly for guiding the use of postoperative chemotherapy.

The method can also be used to monitoring effect of therapy.

66 POSTER DISCUSSION

Phase II Study of ALIMTA (pemetrexed disodium, MTA) Single Agent in Patients with Malignant Pleural Mesothelioma

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ALIMTA is a novel, multi-targeted antifolate that targets several enzymes in the folate pathway necessary for thymidine and purine synthesis. Clinical activity has been demonstrated in multiple solid tumors including lung, breast, colorectal, pancreas, and gastric cancers, and mesothelioma. From April 1999 to November 2000 62 chemonaive patients with histologically proven, advanced mesothelioma not amenable to curative therapy were enrolled in a phase II study to determine the efficacy and toxicity profile of single agent ALIMTA 500 mg/m2 given as a 10 minute i.v. infusion. Treatment was given on day 1 and repeated every 3 weeks. Tumor response was the primary outcome with secondary outcomes including time to event parameters, lung cancer symptom scale, pulmonary function tests, and lung density assessment. After 21 patients had been enrolled, daily low-dose folic acid and vitamin B12 were added to ALIMTA therapy for those patients on study at that time and for all new pts to reduce the risk of severe toxicity associated with ALIMTA.

Results: Patient characteristics included: 87% male, median age 67 yrs. (range 40-80); 74% epithelial type, 9% sarcomatous, 14% mixed, and Stage III = 31%, Stage IV= 54%. The median number of cycles given was 3 (range 1-16). In 62 patients evaluable for response, 9 achieved partial response (PR) (14.5%) (95% C.I. 7-26%). 34 patients had SD (55%) and 13 had PD (21%). To date, the median duration of response is +10.8 months. The median time-to-progressive disease is 5.4 months and median survival time is 10.7 months. The 1-year survival rate is 25%. Of those 45 patients who received folic acid and vitamin B12 supplementation at some point of their treatment, 8 patients responded. Five of these 8 patients received vitamins from the beginning of their treatment while another 3 patients started later. Of the 17 patients who never received vitamins, one patient had a PR. All 62 patients were evaluable for toxicity. Grade 3/4 granulocytopenia, thrombocytopenia, and anemia were observed in (percents) 14/14%, 1.7/0% and 1.6%, respectively. Non-hematological toxicities included fatigue, anorexia, nausea, and febrile neutropenia.