a major factor in treatment decisions, our CE estimate of $48,933 CAD (approximately $30,583 USD) per LYG shows that treatment with DC in this setting is within an acceptable range of cost-effectiveness compared with other healthcare interventions.

777 POSTER

A multi-institutional trial comparing survival of patients with brain metastases from lung cancer treated with temozolomide plus radiotherapy versus radiotherapy alone

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Background: This randomized study evaluated the efficacy and safety of concurrent administration of Temozolomide (TMZ) and WBRT compared to WBRT alone in patients with previously untreated brain metastases from lung cancer.

Material and Methods: Patients with histologically or cytologically proven lung cancer and brain metastases were randomly assigned to treatment with TMZ 75mg/m^2 per day during conventional WBRT 3 Gy /5days per week (total dose 30Gy) or with WBRT alone. Beginning one month post WBRT, patients in WBRT + TMZ received 200mg/m^2 per day for five consecutive days every 28 days for 6 cycles. The primary endpoint was radiological response assessed by CT scan or MRI at 3 months post WBRT.A survival analysis by treatment arm was also performed by different prognostic factors as number of lesions, first diagnosis brain metastases, recursive partitioning analysis (RPA) classes and cause of death (primary site and/or brain).

Results: To date 108 evaluable patients have been enrolled. The groups were similar with respect to age, gender, performance status neurological function score and RPA classes.103 patients have been evaluated for response by radiological assessment (52 in the TMZ and WBRT group; 51 in the WBRT alone group). In the TMZ and WBRT group 48% of patients achieved complete and partial response compared to 27.5% respectively in WBRT alone group(p=0.031)Median follow up was 5.56 months (range0.426-20.79). Median survival was 7.9 months in the TMZ plus WBRT and 4.3 in the control arm (p=0.06) . The median survival in patients with multiple lesions in the study group was 7.3 months versus 4 months in the control group (p=0.1248). The median survival in patients with first diagnosis brain metastases and then lung was 7.4 months in the study group and 4 months in the control group (p=0.013). The median survival in RPA class I was 8 months in the TMZ and WBRT group compared to 8 months in the control group (p=0.78) and in Class II 3.8 months in the study group versus 3.31 in the control group (p=0.05). No grade 3 toxicities were noted.

Conclusion: These data indicate that combination treatment with TMZ and WBRT improves the efficacy of WBRT alone in brain metastases especially in chemotherapy naive patients.

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UPA and PAI-1 are associated with angiogenesis but not prognosis in non-small cell lung carcinoma

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Background. Urokinase Plasminogen Activator (uPA) and Plasminogen Activator Inhibitor type 1 (PAI-1) has been suggested as a prognostic marker in nonsmall-cell lung carcinomas (NSCLC). This study investigates the levels of uPA and PAI-1 in 124 NSCLC, where estimates of tumour angiogenesis have been presented previously.

Materials and methods. UPA and PAI-1 levels were assessed in 119 and 123 frozen tumours, respectively, using a sandwich ELISA method.

Results. Median uPA was 30 ng/mg protein (range, 5-163 ng/mg protein), and median PAI-1 was 34 ng/mg protein (range, 3-286 ng/mg protein). UPA and PAI-1 were significantly correlated, P<0.0001. Both factors were independent of histological type, T and N classification, malignancy grade, stage, age and vascular scores. Evaluated as continuous parameters or in tertiles, neither of the factors were markers of poor prognosis in univariate analysis. Significantly higher levels of uPA and PAI-1, respectively, were seen in tumours with an angiogenic vascular pattern as compared to tumours with an alveolar vascular pattern. In multivariate analysis using overall death as endpoint, high disease stage (P<0.0001), old age (P=0.05) and adenocarcinoma (P=0.002) were identified as the only independent markers of poor prognosis, whereas the angiogenic vascular pattern was borderline significant (P=0.06).

Conclusions. In this study, significantly high uPA and PAI-1 levels were seen in tumours with an angiogenic vascular pattern as compared to tumours with an alveolar vascular pattern. However, neither uPA nor PAI-1 were prognostic markers in univariate or multivariate analyses. We conclude that uPA and PAI-1 are not prognostic markers in NSCLC, but may be involved in angiogenic processes in NSCLC.

779 POSTER

A pilot study of hyperfractionated accelerated radiotherapy (HART) following induction cisplatin and vinorelbine for stage III non-small cell lung cancer (NSCLC).

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Background: Continuous hyperfractionated accelerated radiotherapy (CHART) is superior to radiotherapy alone for inoperable NSCLC. The purpose of this study is to assess the feasibility and efficacy of HART (modified CHART) following induction chemotherapy for stage III NSCLC.

Material and Methods: Thirty patients with stage IIIA/B NSCLC were enrolled between July 1999 and March 2001. The treatment consisted of 2 cycles of cisplatin 80 mg/m^2 on day 1 and vinorelbine 25 mg/m^2 on day 1 and 8 every 3 weeks followed by HART; three times a day (1.5-1.8-1.5 Gy, 4-hour interval) for a total dose of 57.6 Gy in 36 fractions over 2.5 weeks. Patient characteristics: median age 64 (range 46-73), male/female: 24/6, performance status 0/1: 8/22, < 5% weight loss/5% or greater: 25/5, T1/2/3/4: 4/10/1/15, N0/1/2/3: 1/4/18/7, IIIA/B: 9/21, squamous/non-squamous: 13/17.

Results: All patients received 2 cycles of chemotherapy and all but one patient completed HART. Grade 3 or greater toxicities included neutropenia: 25, anemia: 3, thrombocytopenia: 2, infection: 5, esophagitis: 5, nausea: 3, radiation pneumonitis: 3, and dermatitis: 1. There were 2 early deaths due to radiation pneumonitis. The overall objective response rate was 83% (25/30, 95% CI: [65%, 94%]). With a median follow-up period of 33 months in surviving patients, the median survival time was 22 months (95% CI: [13, 34$^+$]) and the 2-year overall survival was 50% (95% CI: [32%, 68%]). The median progression-free survival time was 10 months (95% CI: [8, 20]) and the 1-year progression-free survival was 47% (95% CI: [29%, 65%]). To date we have observed 2 cases with grade 3 subcutaneous tissue toxicity.

Conclusions: HART following induction cisplatin and vinorelbine was feasible and promising. Future investigation employing dose-intensified radiotherapy in combination with chemotherapy is warranted.

780 POSTER

A phase II study of cisplatin (CDDP) and epirubicin (EPI) in malignant pleural mesothelioma (MPM). A study by the European Lung Cancer Working Party (ELCWP).

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Background: A meta-analysis of chemotherapy and immunotherapy in MPM showed that the most active chemotherapy regimen in term of response rate (RR) is a combination including CDDP and adriamycin (ADR) (Berghmans et al, Lung Cancer 2002; 38: 111). EPI demonstrated an activity similar to ADR (9% versus 11% RR) in regimens without CDDP. The aim of this study was to assess the RR and toxicity of CDDP plus EPI in MPM, a combination not reported in the literature.

Material and methods: Eligibility criteria included untreated unresectable MPM, adequate cardiac, renal, haematological and hepatic functions, absence of active infection and presence of assessable lesion(s). After central registration, patients received CDDP and EPI (both at 90 mg/m^2), every 3 weeks for 3 cycles. Stable and responding (WHO criteria) patients were treated until best response or unacceptable toxicity. We used a two-stage optimal design of Simon to determine the number of patients to be

included in the study. If less than 4 responses occurred in the first 19 registered patients, the study should be closed. Otherwise, accrual had to be pursue until a minimum of 55 eligible patients.

Results: 64 eligible patients were registered between 08/1998 and 01/2003. At this time, 56 patients have been evaluated. Their principal characteristics were: median age 62 years (41-78), median Karnofsky performance status 90, stage I/II/III/IV 23/1/12/20, histological type (epitheliomatous/sarcomatoïd/mixed) 33/9/3, male/female 48/8. Among 51 assessable patients, we observed 6 partial responses after 3 cycles. The best overall response rate at 6 cycles was 17.6% (9 PR) (IC 95% 7.1%-28.1%). After 3 cycles, grade III/IV leucopenia and thrombopenia were respectively observed in 48.1% and 0% of the patients. Non haematological toxicity was mild with grade II/III nausea and vomiting in 50% of the patients.

Conclusions The preliminary results of our phase II trial demonstrate the potential activity of the combination of cisplatin and epirubicin in malignant mesothelioma, with an objective response rate of 17.6%. Except for leucopenia, this regimen is well supported and compares adequately with other active combinations

781 POSTER

A randomized phase II trial of gemcitabine and either day 1 or day 8 carboplatin for advanced non-small cell lung cancer (NSCLC)

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Background: Chemotherapy with platinum-containing regimens has been found to produce an improvement in survival and quality of life in patients with advanced NSCLC. The primary objectives of this study were to determine the toxicity and efficacy of gemcitabine (days 1 *and* 8) and carboplatin (on either day 1 *or* 8; Carb d1 or Carb d8 arms) in patients with advanced NSCLC. Secondary objectives included quality of life, duration of response, time to disease progression and survival.

Methods: This was a multi-center, open-label, randomized Phase II study. Eligible patients had histologically or cytologically proven Stage IIIB or IV NSCLC, with ECOG performance status $\leq$ 2. Gemcitabine (1000 mg/m^2) was given as an intravenous infusion over 30 minutes on days 1 and 8 of a 21-day cycle with carboplatin (AUC 5) given as a 1-hour infusion immediately after the gemcitabine infusion on day 1 or day 8.

Results: Forty patients were enrolled in this study, with 20 patients (pts) in each arm (mean age 62 yr; 17 females, 23 males; 9 pts with Stage IIIB disease, 31 pts with Stage IV disease). Reasons for treatment discontinuation were: therapy completed according to protocol (8 cycles) (7 pts), death due to study disease (2 pts), adverse event (1 pt), lack of efficacy/progressive disease (14 pts), patient decision (1 pt), physician decision (14 pts) and protocol violation (1 pt). There were 4 partial responses in the Carb d1 arm and 6 partial responses in the Carb d8 arm, giving an overall response rate of 25%. There were no statistically significant differences between the two arms for median survival time (40.7 weeks in the Carb d1 arm, 39.1 weeks in the Carb d8 arm), time to progression (28 weeks Carb d1, 29.5 weeks Carb d8), or time to treatment failure (14.6 weeks Carb d1, 17.1 weeks Carb d8), and the one-year survival results were similar (27.8% Carb d1, 33.3% Carb d8). The achieved dose intensities of both gemcitabine and carboplatin were significantly higher in the group that received carboplatin on day 1 than in the day 8 group. Toxicities of note included grade 3/4 neutropenia (15 pts Carb d1, 11 pts Carb d8); grade 3/4 thrombocytopenia (14 pts Carb d1, 7 pts Carb d8); grade 3/4 dyspnea (5 pts Carb d1, 3 pts Carb d8); and febrile neutropenia (1 pt Carb d1). Nine patients in the Carb d1 arm, but only one patient in the Carb d8 arm, required a platelet transfusion. There was no clear difference in quality of life, as assessed by the EORTC QLQ-C30 and QLQ-C13 scales after three and six cycles of treatment.

Conclusion: The two gemcitabine-carboplatin schedules were of similar, moderate efficacy in treating patients with advanced NSCLC, however, fewer patients in the arm that received carboplatin on day 8 experienced grade 3/4 neutropenia and thrombocytopenia and required platelet transfusions.

782 POSTER

CPT-11- Gemcitabine as second line chemotherapy in small cell lung cancer (SCLC). A multicentric phase II trial.

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Background: CPT-11 and Gemcitabine have shown activity in SCLC even in pretreated patients (pts). We conducted a prospective phase II study to determine the activity of this combination as second line treatment in pts with SCLC.

Patients and methods: Pts were eligible if they had measurable or evaluable disease, performance status (ECOG) 0-2 and adequate hepatic, renal and bone marrow function. CPT-11 dose was 150 mg/m^2 (90-minute IV infusion) day 1, and Gemcitabine dose was 1500 mg/m^2 (30-minute IV infusion) day 1. Cycles were administered every 2 weeks.

Results: 47 pts were enrolled, 38 male and 9 female. Median age was 64 years (range 42- 78); 91.5% had PS 0 or 1. Twenty-seven pts had sensitive disease and twenty refractory disease (defined as progression within 3 months of starting first-line treatment). A total of 306 courses have been administered (median 6 per patient, range 1 -12).

To date all the pts were evaluable for toxicity and 39 for efficacy. Response rate (RR) was 31% (95% C.I: 17 47.6%), 1 patient with sensitive disease achieved a complete response (2.5%). 33% of pts showed stable disease (SD) and 36% progression (PD). The RR in refractory disease was 22.2%(95% C.I: 6.4 47.7%), SD 38.9% and PD 38.9%. In sensitive disease RR was 38% (95 C.I: 18 61.6%), SD 28.6% and PD 33.3%. Median duration of response was 3 months, median time to progression 6 months (95% C.I: 4.5 7.4 m) and median survival 9.3 months (95% C.I: 5.8 12.8 m).

Toxicity was very mild without grade 3- 4 hematological toxicity. Non-hematological toxicity was also mild, grade 3-4 toxicity including was observed in <1% of cycles (Nausea/ vomiting, asthenia, renal, hepatic or diarrhea). 3 pts developed skin toxicity grade 1-2, and 5 alopecia grade 1 3.

Conclusions: This combination is active as second line treatment of SCLC, showing an encouraging median survival. The profile of toxicity is very mild. Further development of this combination is warranted.

783 POSTER

New EGFR variants around the EGFRvIII region in non-small cell lung cancers(NSCLC)

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Epidermal growth factor receptor (EGFR) is a 170kDa transmembrane glycoprotein and is overexpressed in various human malignancies including NSCLC. While it is a potential target for prevention and therapy, EGFR is also expressed by normal lung. An RNA variant (EGFRvIII) has been described in a number of tumors including NSCLC in which there is an 801bp deletion (exon 2 to 7). This variant has been reported in tumors but has been absent from normal lungs and cell lines. Its absence from normal lung suggests that it may be used as a biomarker or chemotherapeutic target. However, there are few clinical reports on EGFRvIII in lung cancers to date. One immunohistochemical study has found EGFRvIII in 16% of non-small cell lung cancers. While EGFRvIII has been detected by RT-PCR and sequenced in gliomas, prostate cancers, and breast cancers, no similar studies have been carried out in lung cancers so far.

We examined total RNAs from 18 NSCLC cell lines, 6 benign bronchioepithelial primary culture cells, and 48 non-small cell primary lung tumors by RT-PCR (regular RT-PCR or nested RT-PCR) using several primer pairs spanning EGFRvIII (EGFR exon 1-8). When a truncated EGFR variant was present in PCR reaction mixture, we isolated the truncated product from ethidium bromide stained agarose gels and sequenced the cDNA created from the isolated product.

We were unable to confirm the presence of EGFRvIII in NSCLC cell lines, primary tumors, or normal bronchioepithelial primary culture cells. Wild type EGFR was demonstrated in 78% primary tumors, 94% cell lines, and 83% bronchioepithelial primary culture cells. In addition, we found 10 truncated EGFR variants that did not correspond by sequence analysis to EGFRvIII. These new variants were present at variable copy number. They may not be