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A phase I study of concurrent pemetrexed/cisplatin/radiation for unresectable stage IIIA/B non-small cell lung cancer

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Background: Concurrent chemoradiation is the accepted standard of care for most patients with unresectable stage III A/B non-small cell lung cancer (NSCLC) but no standard chemotherapy regimen or schedule has yet been established. Cisplatin, combined with a third generation agent, provides the greatest activity in advanced NSCLC but, to date, no third generation agent has been shown to be tolerable at full dose in combination with radiotherapy (RT) and cisplatin. Pemetrexed/cisplatin (PemC) has shown promising activity in the advanced disease setting and full dose pemetrexed combined with RT or RT/carboplatin appears tolerable.
Methods: From Dec 15, 2005 to Decmber 19, 2006, 10 patients (pts) with unresectable stage IIIA/B NSCLC were entered on three dose levels of a phase I trial evaluating PemC combined with 61−66 Gy RT (date of last follow up February 1, 2007). Eligible patients had <5% weight loss, ECOG PS 0/1, no malignant effusions, FEV1 > 1.3 l and adequate organ function. Pts received two q21 day cycles of PemC (Pem 300, 400 or 500 mg/m^2 day 1, C 25 mg/m^2 days 1−3) concurrent with RT (61−66 Gy over 6 to 6.5 weeks) followed by two consolidation q21 day cycles (Pem 500 mg/m^2 day 1, C 75 mg/m^2 day 1). All pts received dexamethasone premedication and B12/folate vitamin supplementation.
Results: Ten pts were accrued (3 at dose levels 1 and 2, 4 at dose level 3). Demographics: median age – 63 years [range 46−69]; stage IIIA/B – 4/6; PS 0/1 – 2/8; median radiation dose – 65 Gy [range 60.5−66]. One pt had dose reduction of cisplatin for cycles 3 and 4 due to elevated creatinine levels, two pts received only cycles one and two (one due to pt refusal despite only grade 2 toxicity having been observed; one in a pt with pre-existing metal allergies who developed progressive cisplatin allergy). Neutropenia: gr 3 – 0 pts, gr 4 – 2 pts; with fever – 0 pts. One pt on dose level 3 required hospital admission for grade 3 esophagitis but was able to complete all planned concurrent chemoradiotherapy and start consolidation chemotherapy at full dose. Other gr 3 toxicities were uncommon: hypertension (2); diarrhea (1); anemia (1); hyperglycemia (1); hypophosphatemia (1); thrombocytopenia (1). Seven of 8 evaluable pts achieved partial response by RECIST (88%) after independent review with no local progression to date (median f/u 5.3 months). All pts remain alive, with one pt having distant relapse (>12 months after commencing treatment). One pt on dose level 2 in PR was subsequently deemed resectable and was resected 5.5 months after starting study therapy.
Conclusion: Full dose PemC and full dose concurrent RT is well tolerated and preliminary efficacy appears promising. The study is ongoing and has been amended to add a fourth dose level increasing the dose intensity of cisplatin during RT to 20 mg/m^2 daily $\times$ 5 (Pem remains at 500 mg/m^2). A phase II study is planned.

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Efficacy and safety of single-agent axitinib (AG-013736; AG) in patients (pts) with advanced non-small cell lung cancer (NSCLC): a phase II trial

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Background: A correlation between vascular endothelial growth factor (VEGF), microvessel density, and prognosis has been reported in pts with NSCLC. AG is a specific VEGF receptor (VEGFR) inhibitor with picomolar potency against VEGFR 1, 2 and 3. This is an open-label, multicenter phase II study examining the efficacy and safety of single-agent AG in pts with advanced NSCLC.
Methods: Pts with stage IIIB or metastatic NSCLC received AG 5 mg BID. Eligibility criteria included measurable disease and ECOG performance status of 0 or 1. A Simon 2-stage minimax design was used with 18 pts in the first stage plus an additional 14 in the second stage if 1/18 pts responded. The primary endpoint was response rate (RR) according to RECIST.
Results: A total of 32 pts were enrolled: median age was 66.5 yrs (range 39–80); histologies included adenocarcinoma (75%), squamous cell carcinoma (12.5%), and other (12.5%); 59% male/41% female; 78% received prior chemotherapy, 50% prior surgery, 50% prior radiotherapy, 9% investigational therapy, 3% immunotherapy, and 6% were treatment-naive. Mean duration of treatment was 2.6 months (mo) (range 0.03–12.9 mo). Three (9.4%) investigator confirmed responses were reported with a 95% confidence interval (CI) of 2, 25. Median duration of response was 8.3 mo (95% CI: 5.9, 10.6 mo). Median survival was 12.8 mo (95% CI: 9.9 mo, undefined) and progression-free survival was 4.9 mo (95% CI: 3.6, 7.0 mo). 30 (94%) pts discontinued treatment: lack of efficacy 21 pts (66%), adverse events 5 pts (16%), death 2 pts (6%), and other 2 pts (6%). Grade 3/4 toxicities ($\geqslant$5%) were fatigue (22%), hypertension (9%), diarrhea (6%) and hyponatremia (6%).
Conclusions: AG demonstrates single-agent activity in pts with advanced NSCLC. Therapy is well tolerated with manageable toxicity in this population. Further investigation in this setting is warranted.

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Quantitative evaluation of dyspnoea after radiotherapy of non-small cell lung cancer: a prospective study

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Background and Purpose: To evaluate dyspnoea in patients (pts) with non-small cell lung cancer (NSCLC) after radiotherapy (RT) using 3 different self completed questionnaires (SCQ). The goal was linking the scores of subjective dyspnoea with the results of spirometry test (ST) and dose-volume information for normal lung.
Materials and Methods: Pts who were going to have RT for NSCLC were asked to complete EORTC Quality of Life Questionnaire (QLQ-C30) with Supplementary Lung Cancer Module (QLQ-LC13), Cancer Dyspnoea Scale (CDS) questionnaire, and Visual Analogue Scale (VAS) SCQ before starting RT. Higher dyspnoea scores (DS) obtained from the SCQs meant worse dyspnoea. Pre-RT assessment included ST to measure FEV1 and FVC. Percentage of total lung volume irradiated to 20 Gy (V20) was calculated using dose-volume histogram in pts planned for radical RT. SCQs were completed together with same ST at 1, 3 and 6 months follow up (FU) visits, and then every 6 months till disease progression. Post-RT DS and the results of ST where compared to pre-RT values, attributing the latter with “0” level.
Results: Seventy four pts eligible to analysis. Radical RT was given to 35 patients, and 39 pts received palliative RT. At 1 month after finishing RT there was an improvement of dyspnoea score in about 30% of patients using EORTC QLQ-LC13, CDS and VAS. The mean DS remained significantly better at 1 year in pts whose DS improved at 1 months after completing RT compared to those who had no initial improvement (EORTC QLQ-LC13 – $p = 0.003$; CDS – $p = 0.02$; VAS – $p = 0.001$). There was no significant difference between the mean FEV1 changes in patients whose post-RT DS initially improved or not improved using all SCQs studied. The mean FVC was significantly better at all FU intervals for patients with initial improvement of a DS measured by VAS ($p = 0.04$). Radiation pneumonitis grade >2 was more frequent in patients who had no initial improvement of DS using EORTC QLQ-LC13 (11% vs 0%, $p = 0.05$) and VAS (12% vs 0%, $p = 0.05$). Lung V20 above 20% associated with worse dyspnoea measured by EORTC QLQ-LC13 ($p = 0.01$) and VAS ($p < 0.0001$) scales.
Conclusion: A better DS measured at 1 month after finishing RT corresponds with long term improvement. VAS and EORTC QLQ-LC13 are equal in assessing of post-RT dyspnoea. CDS does not seem to add accuracy in post-RT evaluation of dyspnoea.