179 POSTER

Preliminary results of a phase II study of neoadjuvant radiotherapy (RT) concurrent with weekly paclitaxel (P) and carboplatin (C), followed by surgery (S) in patients (pts) with stage IIB–IIIB non small cell lung cancer (NSCLC)

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Purpose: A phase II study was performed to evaluate the efficacy, toxicity and feasibility of RT concurrent with P and C in pts with loco-regionally advanced, stage IIB–IIIB NSCLC.

Patients and Methods: 33 consecutive, non-selected pts were enrolled between February 1998 through June 2000. They were to receive 45 Gy in 25 fractions to the primary tumor, mediastinal and S/C lymph nodes, followed by an off cord "boost" 5.4–25.2 Gy in 3–14 fractions, concurrent with weekly P (45 mg/msq) and C (100 mg/msq). Pts were then re-assessed for S. 33/33 pts are evaluable; the median follow up time is 23.4 months.

Results: Response to neoadjuvant RT/P/C: CR: 3/33 (9%), PR: 12/33 (36.5%), SD: 11/33 (33.5%), PD: 7/33 (21%). There were 3 pathological CRs. 18 pts (54.5%) had curative resections. 14/33 pts (42.5%) developed moderate/severe esophagitis necessitating treatment interruption; Hematological toxicity was mild, and 86% Of the planned chemotherapy cycles were actually given. There was one case of postoperative mortality. Of 18 operable pts, 6 (33.3%) are alive NED at 10+ to 32+ months; 3 (16.7%) are dead due to intercurrent disease, without evidence of malignancy, at 6–22 months; 4 (22%) are alive with disease (AWD), and 5 (28%) are dead of disease (DOD). Of 15 inoperable pts, 10 (66.7%) are AWD and 5 (33.3%) are DOD. The overall actuarial survival is 30% and DFS is 49% at 30 months.

Conclusion: This regimen of neoadjuvant RT concurrent with weekly P/C followed by surgery is effective, well tolerated and feasible for pts with locally advanced NSCLC.

180 POSTER

A prospective, randomized study to compare the value of two fractionation schedules of palliative radiotherapy (RT) for inoperable non-small cell lung cancer (NSCLC)

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Purpose: A prospective randomized study was conducted to compare the value of 2 fractionation schemes of palliative RT for inoperable symptomatic NSCLC. Assessed was the impact of either treatment on the degree and duration of relief of tumor-related symptoms and on patient's performance status (PS). Secondary endpoints included treatment side effects, objective response and overall survival.

Methods: After stratification, 100 patients (pts) from 8 Polish institutions were randomly assigned to 20 Gy/5x/5 days (Arm A) or 16 Gy/2x/8 days (Arm B). There were 90 men and 10 women aged 47-81 (mean 66), PS 1 - 4 (median 2). 84 pts had locally advanced tumor and 16 pts had metastatic disease. Squamous cell carcinoma was diagnosed in 65 pts, adenocarcinoma - in 9 pts, large cell carcinoma -in 1 patient and unspecified NSCLC -in 25 pts. Both pts groups did not differ in the incidence and degree of initial tumor-related symptoms: cough (p=0.17), dyspnoea (p=0.53), haemoptoe (p=0.32), chest pain (p=0.48), dysphagia (p=0.58) and superior vena cava syndrome (SVCS) (p=0.55). Treatment effects were assessed using patient's chart (weekly for 8 weeks), doctor'ss scoring of symptomatic change (monthly) and by chest X-ray (every 2 months).

Categorical data were analyzed with the use of Chi-square test or Fisher's exact test. Mann-Whitney test was used to analyze the differences in treatment effects between study arms. Time to symptomatic progression and overall survival was estimated according to the Kaplan-Meier method.

Results: 55 pts were assigned to Arm A and 45- to Arm B. 98 pts received assigned treatment whereas 2 pts died before the end of treatment. Treatment tolerance was good and did not differ between study arms. Most frequent side effects included dysphagia (respectively 4% and 14%, p=0.33) and oesophagitis (17% and 14%, p=1.00). No significant differences between study arms were observed, respectively 4 and 8 weeks after treatment start, in the degree of relief of dyspnoea (p=0.24, p=0.64), haemoptoe (p=0.51, p=0.70), chest pain (p=0.76, p=0.45), dysphagia (p=0.58, p=0.94) and SVCS (p=0.19, p=0.40). The only significant difference in favor of 20 Gy/5x was noted in the degree of improvement of cough at week 4 (p=0.02), however the difference disappeared at week 8 (p=0.42).

Conclusion: No clinically significant differences in treatment tolerance and efficacy were observed between study arms. Updated results will be presented.

181 POSTER

Tumour necrosis as an independent prognositic marker in non-small cell lung cancer

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Purpose: Extensive tumour necrosis (TN) has been demonstrated to correlate with a poor outcome in a number of different malignancies. In a retrospective study the extent of TN in surgically resected non-small cell lung cancer (NSCLC) was assessed and correlated with clinico-pathological and biological parameters, and patient outcome.

Methods: Tissue specimens from 178 patients who had undergone surgical resection of stage I-IIIA NSCLC with curative intent were studied. The specimens were routinely processed, formalin-fixed and paraffin embedded. Four micrometer sections were cut onto slides and counterstained with haematoxyllin. Two independent observers interpreted TN and differences were resloved using the double-headed microscope.

Results: TN was a univariate prognostic factor (p = 0.0016) of a poor outcome and positively correlated with platelet count (p = 0.004), T-stage (p = 0.001) and p53 expression (p=0.031) with near significant associations with N-stage (p = 0.063) and matrix metalloproteinase (MMP)-9 (p = 0.058). In multivariate analysis TN, N-stage, platelet count and epidermal growth factor receptor (EGFR)/MMP-9 co-expression were independent prognostic factors.

Conclusion: These data suggest that increased TN reflects an aggressive tumour phenotype. More work is required to elucidate the role of TN in tumour progression.

182 POSTER

Phase II trial of BBR3464, a novel, bifunctional platinum analog, in advanced but favorable out-come, Non Small Cell Lung Cancer patients

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Background: BBR3464 is a tri-platinum compound 10-fold more potent than cisplatin (P), and differing from P in its structure, nature of adducts formed, and spectrum of activity in preclinical models. Common toxicities when BBR3464 is given intermittently are granulocytopenia (rarely thrombocytopenia), asthenia, delayed N&V and diarrhea. No neurotoxicity or nephrotoxicity have been observed in Phase I studies.

Method: We are conducting a multicenter Gehan 2-step Phase II study to evaluate the activity of BBR3464 in patients with NSCLC failing a previous P-based regimen. Failure is defined as a radiological or clinical evidence of progressive disease (PD) in patients responding to or stabilized (3 months) after first line treatment. BBR3464 is administered as out-patients at 0.9 mg/m2 every 21 days without pre/post hydration and antiemetic prophylaxis. Patients are evaluated for response according to RECIST criteria every 2 cycles.

Results: Between November 2000 and April 2001, 18 patients (median age 61 years, range 39-79; median PS of 0, range 0-1) were treated. Nine patients are evaluable for toxicity and efficacy. The median time from previous P therapy is 5 months (range 1-11). Preliminary toxicity reported are: febrile neutropenia (G3=1), nausea (G2=1; G1=1), diarrhea (G2=1; G1=1), fatigue (G2=1). No pulmonary toxicity, nephrotoxicity or neurotoxicity have been observed. The median value of granulocytopenia reported in 13 evaluable cycles is 1440 cells/mm3 (range 490-3140), thrombocytopenia median 215 x103 cell/mm3 (range 133-261 x103). One minor objective response was observed while 3 further patients are stable after respectively 15, 10 and 8 weeks.

Conclusions: BBR3464 at 0.9 mg/m2 every 21 days without hydration can be safely administered in NSCLC; the results so far achieved indicate that the hints of activity observed deserve further evaluation.