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Clinical relevance of p53 and k-ras mutations in non-small cell lung cancer (NSCLC)

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Background: Lung cancer cells frequently carry genetic mutations which may potentially affect clinical behavior of tumor. The two most frequent molecular abnormalities accompanying NSCLC include mutations of P53 and K-ras genes, yet their prognostic relevance is a matter of controversy.

Patients and methods: Fresh-frozen tumor samples from 162 NSCLC patients (125 males and 37 females; 96 squamous cell carcinomas, 44 adenocarcinomas, 9 large cell carcinomas and 13 mixed type carcinomas; mean age 61 years) who underwent complete pulmonary resection between 1997 and 1999 were assessed for the presence of P53 and K-ras mutations. Additionally, in 128 patients molecular analysis included histopathologically tumor-free surgical margins. Exons 5 to 8 of P53 gene, and codon 12 of K-ras gene were initially evaluated by PCR/SSCP and PCR/PIRA techniques respectively, followed by sequencing of positive samples.

Results: P53 and K-ras mutations were found in 29% and 38% of tumor samples, respectively. There was no correlation between mutations and major clinical characteristics. Median survival for patients with and without P53 mutations was 31 months and 27 months respectively, and 3-year survival - 46% and 48%, respectively (p=0.59). Median survival for patients with K-ras mutations was 16 months and for those without K-ras mutation median was not reached; 3-year survival probability in both groups was 35% and 54% respectively (p=0.07). Interestingly, in 26% and 43% of patients respectively, P53 and K-ras mutations in tumor cells were accompanied by mutations in surgical margins.

Conclusions: These results suggest a weak adverse impact of K-ras mutations and no prognostic relevance of p53 mutations in operable NSCLC patients. Both mutations occur frequently in surgical margins believed to be negative on light microscopy. The clinical relevance of the last finding is currently being analyzed and will be presented at the meeting.

Small cell lung cancer

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Haematological colony-stimulating factor (CSF) in the treatment of small-cell lung cancer (SCLC). A systematic review of the literature with meta-analysis

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Purpose: To assess the impact on response rate and survival of maintained chemotherapy dose-intensity (DI) or accelerated chemotherapy by G-CSF or GM-CSF administration in SCLC.

Methods: The methodology of the published studies was assessed using the ELCWP and Chalmers quality scales. Combined hazard ratio (HR), for survival, and relative risk (RR), for response rate, were obtained by the Peto method (< 1 for HR and > 1 for RR meaning a benefit for CSF use).

Results: 12 eligible trials, including 2107 patients, were analysed. Overall median ELCWP and Chalmers quality scores were respectively 59.9% and 55.8% (rs=0.70; p=0.01). There was no significant quality difference between positive and negative trials as well for the ELCWP than for the Chalmers scores (p = 0.87). Maintain chemotherapy DI with CSF support, as assessed in 7 trials, demonstrated no favourable effect on response rate (RR = 0.92; 95% CI 0.85-0.99) and survival (HR = 0.95; 95% CI 0.76-1.19). Also, accelerated chemotherapy (5 trials) was not associated with a positive impact on response rate (RR = 1.02; 95% CI 0.94-1.09) and survival (HR =0.82; 95% CI 0.67-1.00).

Conclusions: On the basis of this review, we cannot recommend the routine use of G-CSF or GM-CSF in addition to chemotherapy in the treatment of SCLC.

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Independent review of radiology from a multicentre phase II study evaluating intravenous (IV) topotecan (T) with either cisplatin (C) or etoposide (E) in the first line therapy of extensive disease small cell lung cancer (EDSCLC) by validated response rate (RR)

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84 chemonaive patients (pts) with EDSCLC, not suitable for curative surgery or radiotherapy, were enrolled into this open label, multi-centre, randomised study. Eligible pts were required to give informed consent, and have histologically proven SCLC with bidimensionally measurable lesions, at least 2cm in diameter, on chest radiographs, computed tomography scans or magnetic resonance images. It has previously been shown that lesion evaluation by stringent criteria correlate very closely to overall outcomes [1].

82 patients received study drug -either T 1.25mg/m2/daily x5 as a 30 min iv infusion with C 50mg/mg2 given iv over 3h on d 5 q 21d; or T 0.75mg/m2/daily x5 as a 30 min iv infusion with E 60mg/m2/daily x5 as a 30-60 min iv infusion q 21d.

58 patients were claimed to have responded, 56 have been reviewed to date by at least one independent radiologist. The radiologist was strictly independent of the patient management and blinded to the therapy received. Preliminary clinical data have been shown elsewhere [2] and the response data presented here have been updated to reflect current status. The table summarises the results of these reviews.

Results: Validated Results of Independent Reviews of 56 Claimed Responses:

Treatment arm Total Claimed Responses CR PR SD PD N/A

T + C 28 2 (7%) 23 (82%) 1 (3.5%) 0 2 (7%)

T + E 28 1 (3.5%) 23 (82%) 1 (3.5%) 1 (3.5%) 2 (7%)

The response rate (RR) claimed by the investigators was 68% overall. The RRs which were confirmed and validated by independent review were 61% and 58% for TC and TE arms, respectively. 95% confidence intervals for these RRs are 44.5% to 75.8% for the TC arm, and 42.1% to 73.7% for the TE arm. Of the 46 PRs, 25 (54%) had >90% reduction in disease bulk: 11 and 14 on the TC and TE arms respectively. 24 pts did not respond and were not reviewed. 2 patients' sets of scans were unavailable, precluding review. 6 pts developed PD during treatment: 3 on TC, after courses (c) c4, c6 and c6; and 3 on TE after c4, c6 and c8. In conclusion, these data indicate that both regimens are active according to very stringent radiological criteria. Data are now being observed prospectively to see how they correlate to time to progression and survival.

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The role of surgery in limited disease (LD) small cell lung cancer (SCLC): a retrospective, comparative study

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To assess the role of surgery in SCLC we performed retrospective analysis of survival in two groups of LD patients (pts) treated between 1982 and 1995. One group (67 pts) was managed with complete resection followed by chemotherapy, and the other (67 pts) with conventional non-surgical methods. In the first group the diagnosis of SCLC was established only after the examination of surgical specimen. The non-surgical group was selected using "pair-matched case-control-method out of 176 LD pts potentially suitable for surgery (i. e. no pleural effusion or other local advancement, no supraclavicular lymph node involvement, good PS) but treated with non-surgical approach. Total series included 109 males and 25 females, 20 T1 and 114 T2 disease, 51 N0, 43 N1 and 40 N2 disease. In the surgical group 23 pts received prophylactic cranial irradiation and in the non-surgical group 39 pts received thoracic irradiation. The most important prognostic factors were well balanced between both groups. Median survival in pts treated with and without surgery was 22 months and 11 months, respectively (p<0.001). The two-year and five-year survival rates were 43% and 27% in the surgical group, and 17% and 4% in the non-surgical group.

Significantly longer survival in pts treated with surgery was found in all T and N categories except N2 disease. Local relapse was more frequent in pts treated conventionally (55%) then in surgically (15%, p<0.001). Distant relapse rates were similar in both groups (36% and 40%, respectively). The most common site of metastases in the entire series was CNS followed by liver, lymph nodes, bones, lungs and skin.

We conclude, that surgery may have a positive impact on survival of LD SCLC pts, and a randomized study addressing this issue should be considered.

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Randomized, phase II study of topotecan/paclitaxel versus cisplatin/etoposide in patients with untreated, extensive disease, small cell lung cancer (SCLC)

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Topotecan and paclitaxel are active single agents in the treatment of SCLC. In previous phase II studies, the combination of topotecan and paclitaxel has demonstrated encouraging activity, suggesting that this combination is worthy of further investigation. This phase II study was designed to compare the combination of topotecan (T) and paclitaxel (Px) with the standard front-line therapy of cisplatin (P) and etoposide (E). Eligible patients had bidimensionally measurable disease, ECOG PS 0-2, and adequate bone marrow, hepatic and renal function. Asymptomatic brain metastases were allowed. Recruitment is completed with 151 patients randomized (76 on the TPx arm and 75 on the PE arm), and preliminary results are pending. Demographic baseline characteristics: females/males 36/115; median age 61; median PS=1; elevated LDH 66%. Patients were randomized to receive either TPx: T 1.0 mg/m2/d IV d 1-5 and Px 175 mg/m2 IV d 1 with prophylactic G-CSF 5ug/kg/d SC starting d 6 for all patients; or EP: P 80 mg/m2 IV d 1 with E 100-120 mg/m2 IV d 1-3. Cycles were repeated every 21 days. The primary efficacy variable is objective response rate, which is to be verified by independent, blinded radiologic review.

Response and tolerability data will be available by the time of the meeting.

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Cisplatin-epirubicin-paclitaxel (PET) weekly administration with G-CSF support in extensive SCLC. A SICOG phase II study

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Background: In a previous phase I study (Frasci et al. Br J Cancer 2001 in press) we showed that cisplatin 40 mg/sqm, paclitaxel 85 mg/sqm and topotecan 2.25 mg/sqm could be safely given weekly in presence of G-CSF support, and that an 80% ORR can be achieved in advanced disease with this regimen.

Purpose: We tried to improve the efficacy of the treatment by increasing the dose of paclitaxel (from 85 to 120 mg/m2), and replacing topotecan with epirubicin (50 mg/m2/week). The dose of cisplatin was slightly decreased to 30 mg/m2/week. This regimen at the present doses had already been tested in a large number of breast cancer patients.

Patients and Methods: Patients with extensive SCLC, aged 18-70, with ECOG PS < 2 were considered eligible provided that they had not received prior chemotherapy. They received weekly P, E, and T at the above reported doses for a maximum of 12 cycles. G-CSF was given on days 3-5 of each week. The planned final sample size was of 33 patients, calculated according to the Simon two-stage design (end point was considered the CR, with a p1=30% and p0=10%), but a preliminary analysis was planned after 22 patients.

Results: As of April 9, 2001, 24 patients have been included in the study (median age 61; PS 0-1/2=13/11) for a total of 178 weekly cycles delivered. Twenty-three patients have been considered eligible for toxicity and response since in one case the hystotype resulted to be NSCLC after a careful revision.

Overall, grade 3-4 neutropenia and thrombocytopenia occurred in 7 and 3 patients. One patients died after 1 cycle due to cardiac failure probably related to sepsis. Anemia was the most frequent hematologic side effect, 9 patients requiring at least once red blood cell transfusions. Symptomatic thrombocytopenia was never observed. Nonhematologic side effects were in general moderate. Severe emesis, mild peripheral neuropathy and severe fatigue were observed in 2, 8, and 5 patients respectively. Among the 19 patients who completed at least 6 cycles 5 complete responses and 10 partial responses have been recorded for a 79% ORR [95% CI=54-94].

Conclusions: The cisplatin, epirubicin, paclitaxel regimen is well tolerated and highly active in extensive SCLC patients. The accrual continues until the planned sample size of 33 patients is reached.

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Activity of ZD0473 in small-cell lung cancer: an update in patients relapsing after one prior chemotherapy regimen

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Aims: This Phase II multicenter study was conducted to assess the use of the new generation platinum drug, ZD0473, in patients with small-cell lung cancer who have previously failed one platinum-based chemotherapy regimen.

Methods: ZD0473 (120-150 mg/m2) was administered by a 1-h intravenous infusion on day 1 of each 3-week cycle. Patients were evaluated in two cohorts: (1) drug resistant (relapsed or progressed ≤8 weeks following prior chemotherapy); and (2) sensitive (relapsed or progressed beyond 8 weeks).

Results: In this ongoing trial, 38 patients with a median age of 62 years (range 38-80) have been recruited at present (F:M [15:23 patients]; resistant:sensitive [11:27]; performance status 0-1 [33] and 2 [5]). To date, 93 treatment cycles have been administered: median 2 cycles per patient (range 1-6), with 9 patients receiving ~4 cycles. Overall, 52 cycles were completed without dose reduction or delay, 12 cycles required dose reduction of >20%, and 13 cycles had a delay of ~7 days. Grade 3 or 4 hematologic toxicities (Common Toxicity Criteria) included thrombocytopenia (grade 3 [7 patients]; grade 4 [9]) and neutropenia (grade 3 [7]; grade 4 [1]). The most frequent grade 3 or 4 non-hematologic event was dyspnea (grade 3 [4]), irrespective of causality. Two patients withdrew due to hematologic toxicity. Response to treatment was evaluable in 6 resistant patients: 1 patient had a partial response and 5 patients had progressive disease. Of 21 evaluable sensitive patients, 2 patients had a partial response, 11 had stable disease (including 6 with some evidence of tumor shrinkage) and 8 had disease progression. Across the entire study population, 7 patients had an improvement in WHO score at endpoint. To date, 10 of 25 patients have died due to disease progression. Updated survival data will be presented.

Conclusion: ZD0473 had a manageable tolerability profile and there was a favorable response to treatment in terms of tumor response and stable disease, in both platinum-sensitive and -resistant patients.

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Paclitaxel and Gemcitabine for refractory or relapsed small cell lung cancer (SCLC). A multicentric phase II study

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Paclitaxel and gemcitabine have shown activity in SCLC, as single agent or in combination with others drugs, in untreated and even pretreated patients. Paclitaxel ® gemcitabine seems to be an attractive combination to explore in SCLC. We conducted a prospective phase II study to determine the activity of this combination as second line treatment in SCLC.

Patients and Methods: Patients were eligible if they had measurable or evaluable disease, performance status (ECOG) 0-2 and adequate hepatic, renal and bone marrow function. Paclitaxel dose was 175 mg/m2 (3 hour infusion)on day 1 and gemcitabine 1250 mg/m2 (30 minute infusion)on days 1 and 8. Cycles were administered every 3 weeks.

Results: 41 pts were enrolled, 37 male and 4 female. Median age was 62 years (range 42- 79); 83% had PS 0 or 1 and 17% PS 2; 17 pts had refractory disease (defined as progression within 3 months of starting