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

J. Jassem[1], E. Jassem[2], J. Skokowski[3], G. Kobierska[4], A. Badzio[1], P. Barski[5], J. Jakobkiewicz[5], A. Szymanowska[2], M. Skrzypski[2], K. Sosinska[1]. [1] *Medical University, Dept. of Oncology and Radiotherapy, Gdansk, Poland;* [2] *Medical University, Dept. of Pneumonology, Gdansk, Poland;* [3] *Medical University, Dept. of Chest Surgery, Gdansk, Poland;* [4] *Medical University, Dept. of Pathology, Gdansk, Poland;* [5] *University, Dept. of Molecular and Cell Biology, Gdansk, Poland*

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

T. Berghmans[1], M. Paesmans[1], J.J. Lafitte[2], A.P. Meert[1], C. Mascaux[1], F. Lemaitre[1], J.P. Sculier[1]. [1] *Institut Jules Bordet, Internal Medicine, Bruxelles, Belgium;* [2] *CHU Calmette, Pneumology, Lilles, France*

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)

S. Gwyther[1], E. Quoix[2], P. Cardenal[3], K. Mattson[4], M. Lymboura[5], G. Ross[5]. [1] *East Surrey Hospital, Radiology Department, Redhill, UK;* [2] *Hospices Civils, Strasbourg, France;* [3] *Institut Catala D'Oncologia, Spain;* [4] *Helsinki University Central Hospital, Helsinki, Finland;* [5] *GlaxoSmithKline Pharmaceuticals, Oncology, Harlow, UK*

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

A. Badzio[1], J. Jassem[1], K. Kurowski[2], H. Karnicka-Mlodkowska[1]. [1] *Medical University of Gdansk, Oncoogy&Radiotherapy, Gdansk, Poland;* [2] *Medical University of Gdansk, Thoracic Surgery, Gdansk, Poland*

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.