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Accelerated high-dose radiotherapy by target splitting for inoperable non-small cell lung cancer: a phase I trial

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Background: To determine toxicity of accelerated high-dose radiotherapy (RT). Second endpoint: survival, locoregional control.
Material and Methods: 04/2002 – 04/2003: 30 consecutively referred, not selected patients with histologically/cytolocically proven inoperable, locoregionally confined NSCLC. Stage I: 7 pts., II: 3 pts., IIIA: 12 pts., IIIB: 8 pts. Squamous cell carcinoma: 16 pts., adenocarcinoma: 9 pts., NSCLC not otherwise specified: 5 pts. M/f = 21/9. Only 2 Patients have been staged by FDG-PET scan.
The majority of the patients have been treated by the conformal technique of target splitting. Dose to primary sites: 84.6 Gy ICRU median (75.6 – 90.0 Gy), nodes 63.0 Gy median (59.4 – 72.0 Gy), elective nodes 45.0 Gy. Single fraction size 1.8 Gy, twice daily, 5 days/week, interval 11h (10–12h), treatment duration 35 days median (30–43). For planning 'slow' CTs have been used (4 sec/slice), patients freely breathing, 7 mm margins from GTV to PTV.
In 19 patients' chemotherapy before RT was given, 2 cycles median; no concurrent chemotherapy. Median follow-up of patients alive: 33.5 months (26–37 m).
Results: Acute non-hematologic toxicity (until 6 months after the end of RT): esophagus grade 1: 13 pts., grade 2: 2 pts.; lung: no patient >grade2. No chronic toxicity >grade1. No fatal pulmonary hemorrhage. Overall actual 1-, 2-year survival rate: 73%, 63%, respectively, median 26.3 months. Respective figures for 11 patients IIIA-N2: 82%, 73%, median survival not reached. 5 patients died of intercurrent diseases (3 of these were stage I – patients) 9 patients recurred locally (8 of these presented initially with tumor-caused atelectasis). 4 regional recurrences (2 of them in supraclavicular sites, initially not treated).
Conclusions: Accelerated RT with doses up to 90 Gy in twice daily fractions of 1.8 Gy, delivered mostly by the conformal technique of target splitting shows low toxicity. Survival and locoregional tumor control are encouraging. A trial studying tumorsize-dependant doses has been started.

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Phase II trial of topotecan plus gemcitabine in previously treated small cell lung cancer (SCLC) patients: an Alpe-Adria Thoracic Oncology Multidisciplinary group study (ATOM 012)

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Background: Single-agent topotecan has proven active in the treatment of second-line small cell lung cancer (SCLC) with response rates up to 14% in chemotherapy-refractory patients and up to 38% in chemotherapy-sensitive patients. The role of topotecan in combination with another active agent may be still clarified and may provide further improvement.
Methods: In this phase II trial we evaluate the activity and toxicity of topotecan (1 mg/sqm iv d1–5) plus gemcitabine (1250 mg/sqm iv d1) in relapsed or progressing SCLC patients. Treatment is repeated every 4 weeks up to a maximum of 6 cycles. Eligibility criteria include: histologically or cytologically confirmed SCLC; documented progressive disease after at least 1 prior chemotherapy regimen; age >18 yrs; ECOG PS 0–2; measurable disease (RECIST); no prior treatment with topotecan or gemcitabine; adequate hematologic, hepatic and renal function; written informed consent. Brain metastases are allowed.
Results: To date, 37 patients have been enrolled. Patient characteristics: median age, 64 yrs (range 35–77); male/female, 29/8; ECOG PS 0/1/2, 10/17/10 patients; 61% patients had sensitive disease (recurrence >3 months after first-line chemotherapy) and 39% patients had refractory disease (failure <3 months after first-line chemotherapy). Thirty-six patients had received prior platinum-based therapy involving etoposide and either cisplatin or carboplatin. Ninety-nine cycles have been delivered (median 2, range 1–6). All patients are evaluable for toxicity. Grade 3–4 toxicities include 54% neutropenia, 16% anemia, 46% thrombocytopenia, 13% neutropenic fever, 27% fatigue. One toxic death was observed. One patient (3%) obtained complete response and 8 patients (22%) obtained partial response, for an overall response rate of 24%; SD was observed in 7 patients (19%), PD in 15 patients (40%). Four early deaths were reported; 2 patients are currently on treatment. At the time of this analysis median time to progression is 7.7 weeks. Median survival time is 16.3 weeks, and 1-year survival rate is 11%.
Conclusions: Based on these preliminary results, the combination of topotecan and gemcitabine is active and has an acceptable toxicity profile in previously treated SCLC patients. However, it is unlikely that the addition of gemcitabine improves the outcome compared to single agent topotecan.

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Telomere biology and DNA-repair systems in non-small cell lung cancer

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Background: Telomeres and telomerase perform important roles in suppressing or facilitating malignant transformation. Moreover, recent "in vitro" observations propose that telomere-binding factors may be ancient and general DNA-repair factors that have been exploited by the cell to protect telomeres. Our aim consists of investigating telomere biology in non-small cell lung cancer (NSCLC) in relation to genome integrity.
Material and Methods: Sixty-two NSCLCs were evaluated to establish telomere status. Thus, we studied terminal restriction fragment (TRF) length and telomerase activity. Following, we performed expression analyses by using a human microarray in which 96 genes related to the different DNA repair systems have been included. This study was established by comparing gene expression in two subgroups of cancers, the first one maintaining telomeres, and the second one showing a significant telomere shortening.
Results: Overall, telomere length in NSCLCs was 8.12±0.37, with no significant differences to values detected in non-tumor samples (7.84±0.21) (P = 0.401). Telomerase activity was detected in 54 (87%) tumors, and no significant differences were found in relation to telomere length. As comparing with control samples, 32 tumors (51.6%) showed telomere maintenance, and 20 (48.4%) telomere shortening (>20%). Kaplan-Meier survival curves indicated important prognostic differences between both groups, the group of cancers displaying telomere shortening conferred a significant poorer clinical evolution (P = 0.02). Results from microarray expression analyses suggested significant changes for a number of genes regarding to telomere status. The major differences seems to concern to *PARP-1* and *PMS6*. Whereas *PARP-1* is overexpressed in most of NSCLCs with telomere maintenance, *PMS6* overexpression seems to be associated with telomere shortening.
Conclusion: These observations lead us to draw an interaction between DNA repair and telomere function.

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Involvement of Akt/PKB signalling in survival of cisplatin-sensitive and -resistant human pulmonary mesothelioma cells

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Background: It is shown that Akt/Protein kinase B (PKB) is constitutively active and promotes survival and resistance to chemotherapy in several non-small cell lung cancer cell lines. PI3-kinase can activate Akt/PKB, and Akt/PKB can exert antiapoptotic effects through phosphorylation of members of the apoptosis-regulating Bcl-2 family. We determined the importance of Akt/PKB in survival of the human pulmonary mesothelioma cell line P31 wt (wt) and the cisplatin-resistant subline P31 res1.2 (res1.2).
Methods: The cell lines were exposed to 25 or 50 μM LY294002 (LY), a PI3-kinase inhibitor, for 30 min, 2 or 6 h. The phosphorylation of Akt 1 at S473 (P-Akt) was determined by Western blot (WB), and effects on apoptosis induction was determined by TUNEL staining and caspase activity assays. Preliminary WB analysis of Bcl-X(L) and Bcl-2 expression was also performed. All experiments were performed in medium with 10% serum.
Results: Both cell lines expressed Akt 1 and P-Akt under control conditions at all times examined. Exposure to 25 μM LY did not inhibit P-Akt in either cell line, and 50 μM was inefficient in res1.2 cells. In wt cells, 50 μM LY inhibited P-Akt after 30 min, but not after 2 or 6 h exposure. An increase in the number of TUNEL positive wt cells was found after 30 min and 2 h, but not 6 h, exposure to 25 and 50 μM LY. No changes in number of TUNEL positive cells were found in res1.2 cells at any exposure. Caspase-3 activity but not caspase-8 or -9 activities increased after 6 h exposure to 25 and