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Current phase II data for ZD0473 in patients with mesothelioma who had relapsed following one prior chemotherapy regimen

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Aims: To examine the tolerability and efficacy of ZD0473, a new generation platinum drug, in patients with mesothelioma who have relapsed after prior chemotherapy.

Methods: Patients were administered ZD0473 by 1-h iv infusion on day 1, at a dose of 120-150 mg/m2, given every 3 weeks, in this Phase II, open-label, multicentre trial.

Results: At this interim analysis, 41 patients had been recruited for the study (F:M [5:36 patients]; performance status 0-1 [31] and 2 [10]; median age 59 years [range 37-75]). In total, 34 patients had received prior cisplatin or carboplatin therapy, the other 7 patients had mainly received either cyclophosphamide or mitomycin C. Time since last treatment was 0-3 months (9 patients), 3-6 months (11), 6-12 months (10), >12 months (4). To date, 91 treatment cycles have been completed (median 2 cycles per patient, [range 1-6]); 6 patients received ~4 cycles. Four patients required treatment delay due to toxicity, only one patient had a delay of ~7 days. Toxicities were experienced by all patients, but were mostly mild in intensity. The most commonly occurring haematological toxicity was grade 3 or 4 (Common Toxicity Criteria) thrombocytopenia (grade 3 [6 patients]; grade 4 [5]). The most common non-haematological events were dyspnoea (grade 3 [7]; grade 4 [3]) and chest pain (grade 3 [6]), irrespective of causality. Overall, 25 patients were evaluated for tumour outcome and 14 had stable disease (including evidence of tumour shrinkage in 3 patients). An improvement in WHO performance status score was observed in four individuals.

Conclusion: The toxicity was manageable and the antitumour activity was mainly seen in terms of disease stabilisation. Continued follow up for response and time to progression is ongoing.

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In vitro schedule dependency in the formation of topoisomerase I and II inhibitor and DNA cleavable complexes

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Topoisomerase targeting chemotherapy is an excellent strategy in lung cancer treatment. We studied that cytotoxic effects of combination use of topoisomerase I inhibitor SN-38 and topoisomerase II inhibitor etoposide (VP-16) were evaluated against the non-small cell lung cancer cell line, Ma-1 and small cell lung cancer cell line, SBC-3 using MTT assay and isobologram analysis. For the mechanism of time dependent antitumor activities, we investigated cleavable complexes of topoiosmerase I and II to DNA using in vivo immunodetection assay. The cells were concurrently or sequentially exposed to drugs for 30 minutes, 2 hours and 24 hours with a total culture time of 7 days. The IC50s in 24 hours exposures for SN-38 and VP-16 were 6325 nM and 54.1μM for in Ma-1 cells, respectively. In SBC-3 cells, the IC50s for SN-38 and VP-16 were 1.36 nM and 0.25μM, respectively. In Ma-1 cells, the short time simultaneous and sequential exposure of VP-16 followed by SN-38 showed antagonistic interaction. However, the long time simultaneous exposure, VP-16 followed by SN-38, and all schedules of SN-38 followed by VP-16 were synergistic interaction. In SBC-3 cells, all schedules showed synergistic interaction. Regarding the cleavable complex, both drugs formed the cleavable complex each other within 30 minutes. In VP-16 exposures, the cleavable complex stabilized along 24 hours. However, the cleavable complex dissociated in 6-8 hours with SN-38 continuous administration along 24 hours. The combination of SN-38 and VP-16 also observed this phenomenon in 24 hours exposure. After drugs washed out with various concentrations and times, the cleavable complex dissociated within 2 hours. These findings suggest that SN-38 preceding VP-16 regimen may be the most favoring regimen, because topoisomerase I to DNA complex was dissociated before VP-16 was administered. Furthermore, prolonged simultaneous exposure may be obtained similar effects. Our results may provide a rationale for the design of administration combining topoisomerase I and II inhibitors.

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Interleukin-2 in combination with tamoxifen in malignant pleural mesothelioma

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Purpose: Malignant pleural mesothelioma is a rare disease, closely associated to asbest exposure. The naturally chemoresistant tumor has a median survival ranging from 4 to 18 month. In vitro experiments and phase I/II trials with intrapleural Interleukin-2 (IL-2) have shown promising results assumed to be based on natural killer cell mediated immunity.

Methods: We treated outpatient based 25 malignant pleural mesotheliomas in our department, with IL-2 in parallel with Tamoxifen (TAM). Patients received 120mg TAM daily (day 1-7) and 6 Mio. IU IL-2 subcutaneously (day 4-7) every two weeks. Patients were instructed in selfadministration at home and follow up was performed in the outpatient department every 2 month. The patients characteristics: 22 male and 3 female patients; 9 patients in 1st-, 5 in 2nd-, 6 in 3rd-, 5 in more than 3-lines of treatment. In 17 patients we determined occupational disease with asbest exposure. The median age was 57 years. At onset of IL-2 and TAM therapy 2 patients were Butchart stage I, 16 stage II, 5 stage III and 2 stage IV. Relapsing patients received cytostatic treatment, or palliative irradiation.

Results: The median survival is 15,1 month. 19 patients died (5,3 to 92,6 month) while 6 patients are still alive (14.1 to 102.2 month), 2 of them in an objective response, 3 in stable disease. From all 25 patients 3 had a partial response, 7 stable disease, and 15 progressed under therapy. Toxicty was acceptable with local skin rash. As the patients administered IL-2 in the evening, flue-like symptoms were (during sleep) without detrement to patients.

Conclusion: IL-2 combined with TAM offers an additional chance in the outpatient treatment of malignant mesothelioma. Prospective multicenter trials have to verify these results.

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Varying CD97 expression in lung carcinomas and tumour cell lines

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Expression of CD97, a leukocyte differentiation antigen and member of the EGF/TM7 superfamily, has been shown to correlate with the stage of differentiation and metastasis in thyroid carcinomas. The molecule shows structural homology with adhesion molecules, and may thus also be involved in invasive growth and metastasis of other tumours.

First, 5 lung carcinoma cell lines were examined for CD97 expression by FACS analysis. The NCI-H82 and NCI-H69 cell lines of the small-cell lung carcinoma (SCLC) showed no CD97 expression, whereas all non-SCLC (NSCLC) cell lines (A 549, LCLC 103, EPLC 272) were CD97+. The results were confirmed at the mRNA level.

Second, 44 NSCLC of various histophenotypes and their corresponding normal tissues and 10 SCLC were examined for CD97 by immunohistology. Two different CD97 monoclonal antibodies (mab) were used: CD97EGF detects an epitope at the first EGF-like domain of the molecule, whereas CD97stalk binds to the stalk region right before the transmembrane region. An immunoreactive score was set up based on the method devised by Remmele (RS 0-12) and a correlation with the clinical data of the patients was sought. Soluble CD97 (sCD97) was preoperatively determined in the sera of the patients by ELISA.

CD97EGF was only detected at low levels in 10/44 (mean ± SEM; RS 2.3 ± 0.2) NSCLC. We found a different distribution within the various histophenotypes with a tendency towards adenocarcinoma being more than squamous lung cell carcinoma. The corresponding normal bronchiolar epithelium was completely CD97EGF-. In contrast, the CD97stalk epitope was found in 32/44 (RS 5.4 ± 0.5) NSCLC. Scattered cells within one tumour (11/44) were more strongly positive for CD97stalk (RS 7.6 ± 0.8) compared to those grown in tumour cell formations. In a third of all cases, basal cells of the normal bronchiolar epithelium showed a strong staining for CD97stalk, whereas the upper cells were CD97stalk-. The biopsies of SCLC were CD97- for both epitopes, only 1/10 showed a weak staining for CD97stalk. Tumour stage (AJCC) and preoperatively determined sCD97, CYFRA21-1, SCC, CEA and CA19-9 in the sera of the patients showed no correlation with the expression of CD97 in the tumours.

Taken together, only NSCLC and their derived cell lines were CD97+. The different epitopes of the molecule showed varying distributions within these tumours. SCLC and corresponding cell lines did not express CD97.

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Analysis of MAC-2 binding protein/90k expression in lung cancer

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Purpose: Mac-2 binding protein (Mac-2BP/90K) has been reported to induce the overexpression of MHC and cell-adhesion molecules on cultured tumor cells and to be overproduced in patients with various types of cancer and viral infection. Therefore, this protein is thought to play a crucial role in cellular immune responses in hosts. In this study, we analyzed the expression of Mac-2BP/90K in cultured lung cancer cell lines and tumor tissues from patients with primary lung cancer, and its immunogenicity as a tumor antigen.

Methods: Six lung cancer cell lines and 28 tumor tissues from lung cancer patients were examined for Mac-2BP/90K mRNA expression by Northern hybridization. Sera from cancer patients (n=18) and healthy donors (n=6) were studied for their reactivity to Mac2-BP/90K peptides by ELISA.

Results: Five of 6 (83%) cancer cell lines and 17 of 28 (60.7%) tumor tissues were shown to express high levels of Mac2-BP/90K mRMA. Serum levels of antibodies to Mac-2BP/90K peptides were elevated in 3 of 18 (16.7%) patients but in none of the healthy donors.

Conclusion: Mac-2BP/90K is suggested to be abundantly expressed in lung cancer cells, and to be sufficiently immunogenic to elicit humoral immunity specific for this molecule in cancer patients. Mac-2BP/90K is expected to be useful as a tumor antigen in immunotherapy for lung cancer.

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Neoadjuvant chemotherapy and extrapleural pneumonectomy (EPP) for malignant pleural mesothelioma (MPM)

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Objective: Pilot study to examine the tolerance and outcome of a pre-operative chemotherapy followed by EPP in patients (pts) with potentially resectable MPM.

Patients and Methods: From May 1999 to June 2000, 16 pts were evaluated by an interdisciplinary team for a multimodality therapy consisting of 3 cycles of preoperative chemotherapy with cisplatin (80 mg/m^2 day 1 every 28 days) and gemcitabine (1000 mg/m^2 days 1, 8 and 15), followed by EPP with or without radiation therapy to the area at risk.

Results: The cohort included 1 woman and 15 men with a median age of 57 years (range 48 to 68). Fifteen pts received all 3 cycles of chemotherapy. Major toxicity was haematological. The dose of gemcitabine had to be reduced due to thrombocytopenia in 15 of 47 cycles. Response was evaluated by CT scan. Seven pts had partial remission (43%), 5 no change (31%) and 4 disease progression (25%). Thirteen pts (82%) underwent an EPP. Two pts with progressive disease were not operated on and one pt with no change had only an explorative thoracotomy. Eleven pts had pure epithelial cell type tumors. In one pt the diagnosis of MPM could not be confirmed. Hilar or mediastinal lymph nodes were involved in 3 pts. There was no perioperative mortality. Major perioperative complications included atrial fibrillation (2 pts), acute coronary syndrome (1 pt), chylothorax (2 pts) and bronchial fistula (1 pt). All complications were treated successfully. Ten pts received postoperative radiotherapy. One pt died 7 weeks after EPP from suspected pulmonary embolism. Two pts died from relapse 11 and 19 months after initiation of chemotherapy. Four pts are alive with relapse occurring 9, 13, 15 and 18 months after start of treatment. Six pts are alive without evidence of recurrent disease. At one year, overall and event-free survival is 72% and 65%, respectively. The median survival and event-free survival is 19.4 and 15.4 months, respectively. Up dated results will be compared to our previous series of surgery, followed by chemotherapy and radiotherapy.

Conclusion: Chemotherapy with cisplatin and gemcitabine is effective in earlier stages of MPM. EPP after preoperative chemotherapy is feasible in the hand of an experienced surgeon. Treatment related complications in the perioperative period are manageable. Toxicity is acceptable and is comparable with our results of the trimodality therapy with postoperative chemotherapy. Based on this result we initiated a multicenter phase II study within the SAKK focusing on quality of life issues.

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A prospective infection survey in patients with lung cancer admitted to a cancer hospital

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Purpose: To delineate more precisely the nature and sources of infection in lung cancer patients.

Methods: All patients with lung cancer admitted into a cancer university hospital and developing any infection were included in a prospective survey. Characteristics of the patients, type and source of infection, antibiotherapy and outcome were registered.

Results: 277 patients developed 440 infectious episodes between January 1997 and January 2001. Bacteremia occurred in 8.2% of the cases; Gram positive bacteria, mainly staphylococci and streptococci, accounted for the majority of the documented pathogens (70.7%). The majority of the documented infections originated from the lung (55.5%). They consisted mainly in bronchitis (55.3%) and pneumonia (38.9%). The most frequent pathogens isolated from the airways were Haemophilus influenzae (34.8%), Streptococcus pneumoniae (10.9%), Staphylococcus aureus (8.5%), Moraxella catarrhalis (7.5%) and Pseudomonas aeruginosa (7%). Gram negative bacteria accounted for the majority of documented pulmonary infectious episodes (75.1%). Except for ampicillin resistance in Moraxella catarrhalis (80%), few bacteria were resistant to conventional antibiotherapy.

Conclusion: Our study confirms the importance of lung as a source of infection in lung cancer patients. If needed, empirical antibiotherapy must have adequate activity against Gram positive bacteria

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Combination effects of amrubicin, a novel anthracycline, with cisplatin on human lung cancer cells

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Amrubicin is a novel completely synthetic 9-aminoanthracycline derivative and its C-13 alcohol metabolite, Amrubicinol, inhibits purified human topoisomerase II (topo II). We examined the effect of combination with Amrubicinol and cisplatin (CDDP) in vitro using small cell lung cancer cell line (SBC-3) and adenocarcinoma cell line(Ma-1), using WST assay and analyzed by isobologram. Both drugs used together simultaneously and consequently, the combined effects were additive interaction both simultaneous and sequential administration. A high concentration of CDDP (300 maikuro M) enhanced the topoisomerase II inhibitory activity of Amrubicinol determined by DNA decatenation assay. On the other hand, Amrubicinol increased formation of DNA interstrand cross-links (ICL) on the cells, which analyzed using ethidium bromide binding fluorescence assay when we observed by simultaneous exposure to CDDP (0-30 maikuro M) and Amrubicinol (2 maikuro M) compared with CDDP alone. These biological interactions might result in synergistic interaction between Amrubicinol and CDDP.

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Ifosfamide, mesna and interferon alfa combination therapy in malignant mesothelioma: results of a single center in central Anatolia, Turkey

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Purpose: Malignant mesothelioma (MM) is a serious clinical problem in Central Anatolia due to environmental exposure to asbestos and erionite. MM is an agressive tumor and management is difficult. The purpose of study was to determine the efficacy of ifosfamide, mesna and interferon alfa combination therapy in MM patients.

Methods: The patients with histopathologically confirmed MM received a combinaton of Ifosfamide 3g/m2 1-3 days, uroprotective agent Mesna 3g/m2 1-3 days every 3 weeks and Interferon alfa (IFN) 4.5MU 3 days a week for 6 months as first line chemotherapy.