The Use of Metformin and the Incidence of Metastases at the Time of Diagnosis in Patients with Lung Cancer and Type 2 Diabetes

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investigated the potential use of COX-2 inhibitors in cancer proliferation and apoptosis.

Methods: Celecoxib, rofecoxib, etoricoxib, meloxicam, ibufrofen and indomethacin are the COX-2 inhibitors included in this study. Docetaxel and Cisplatin are the chemotherapeutic agents that we combined with COX-2 inhibitors. Lung cancer cell lines (NCI-H1048-Small cell lung cancer, A549- Non-small cell lung cancer) were purchased from ATCC LGC Standards. At indicated time-point, following 24h and 48h incubation, cell viability and apoptosis were measured with Annexin V staining by flow cytometry. Statistical analysis was performed by GraphPad Prism (version 6).

Results: In Small cell lung cancer cells, following 24h incubation, combinations of docetaxel and meloxicam, docetaxel and ibuprofen, docetaxel and indomethacin, showed increased apoptosis when compared to docetaxel alone ($p<0.0001$). In Non-small cell lung cancer cells, the 24h incubation was not enough to induce satisfactory apoptosis, but following 48h incubation, docetaxel plus indomethacin showed more cytotoxicity when compared to docetaxel alone ($p<0.0001$). In addition, the combination of cisplatin plus indomethacin was the only combination to be found with higher cytotoxicity when compared to cisplatin alone after 48h treatment ($p<0.0001$).

Conclusion: Depending on the drug, the synergistic effect of COX-2 inhibitors plus chemotherapeutic agents has been demonstrated in lung cancer. Our suggestion is that COX-2 inhibitors could be used as additive and maintenance treatment in combination to antineoplastic agents in lung cancer patients.

Keywords: in vitro, lung cancer, COX-2 inhibitors

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The Use of Metformin and the Incidence of Metastases at the Time of Diagnosis in Patients with Lung Cancer and Type 2 Diabetes

Topic: Targeted Therapy

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Background: Lung cancer is often insidious disease. It usually produces only a few symptoms until the disease is advanced. At initial diagnosis 20% of patients have localized disease, 25% of patients have regional metastasis and 55% of patients have distant spread of disease. Metastasis is a process by which a small number of cancer cells undergo numerous alterations, which enables them to form secondary tumors at another and often multiple sites in the host. Recently, studies have suggested that cancer stem cells are the originators of metastasis. Cancer stem cells are small populations of slowly dividing, treatment — resistant, undifferentiated cancer cells that are being discovered in a different cancers. Metformin has proved to be effective in the treatment of glioblastomas and neuroblastomas, in vitro, by targeting their cancer stem cell population. Recently, studies have shown that metformin use is not associated with a decreased risk of lung cancer in patients with type 2 diabetes, but it has been suggested that metformin use is associated with improved survival among patients with stage IV NSCLC patients.

Methods: The aim of our study was to compare incidence of metastasis in lung cancer patients (NSCLC and SCLC) that were treated with metformin and patients with lung cancer that were not treated with metformin. It is a retrospective analysis of lung cancer patients diagnosed at our department between January 1, 2012 and December 31 2013 and data were collected from our computerized base.

Results: During the two-year period in our department there were 335 newly diagnosed lung cancer patients. Among them there were 25 (7%) patients with diabetes mellitus that were on therapy with metformin prior to lung cancer diagnosis for at least six months. We have proved significant difference between two groups in the incidence of patients with distant spread of disease (stage IV) at the time of diagnosis. Metformin group had a lower incidence of stage IV at the time of diagnosis (44% vs 64%; $x2 = 4.14$; $p=0.041$). The results did neither reveal a significant difference in total number of patients with distant spread nor in the type of metastasis.

Conclusion: We have shown that patients that were treated with metformin had lower incidence of distant metastases at the time of diagnosis. Further research should evaluate biologic mechanisms and test the effect of metformin on inhibiting the cancer spread in prospective clinical trials.

Keywords: SCLC, NSCLC, Metastases, metformin