Characterization of Malignant Pleural Mesothelioma: Possibilities for an Individualized Therapeutic Arsenal

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ABSTRACT

Less than 50% of malignant mesothelioma patients respond to standard chemotherapy treatment and there is a great need to identify these patients, and find their best treatment options. The aim of this thesis was to increase the understanding of drug sensitivity in malignant pleural mesothelioma.

We studied six mesothelioma cell lines with different phenotype and growth characteristics. The apoptosis signaling mechanism after treatment with selenite was evaluated in two of the cell lines. The drug sensitivity to selenite, bortezomib and four conventional drugs, together with their expression of potential predictive markers was evaluated in all six cell lines with WST-1 and immunocytochemistry. We followed the development of resistance to pemetrexed and carboplatin treatment in a patient with a genome-wide analysis as well as studying specific proteins through silencing, immunohistochemistry and measuring serum levels in the patient. Pleural effusions containing primary malignant mesothelioma cells were received from 18 patients and we characterized and tested their sensitivity to 32 different drugs in a robotized ex vivo assay. Primary cells were further characterized by immunocytochemistry to evaluate the amount of malignant cells and to study the RRM1 and ERCC1 reactivity.

The apoptosis and loss of mitochondrial membrane potential induced by selenite treatment was described and presents a complex signaling pattern. In samples from the drug resistant patient we observed that genes involved in the metabolic processes of pyrimidine and purine were upregulated and immunoreactivity of EMA and cytokeratin 7 was increased at resistance. Silencing of NT5C gene did not induce pemetrexed sensitivity in cell lines and levels of serum mesothelin related protein and carcinoma antigen 125 in serum correlated to the tumor burden.

Selenite affected four out of six mesothelioma cell lines, and was in combination with bortezomib cytotoxic to all six. Epithelioid cells were more sensitive to the different drug and drug combinations than the sarcomatoid cells. Pemetrexed induced an extensive S-phase arrest in affected cell lines. The MRP-1 immunoreactivity of cell lines predicted carboplatin sensitivity and xCT predicted pemetrexed effect.

Large individual variability was observed in the drug sensitivity of the primary cells. The cell isolates were affected by between one and ten drugs and actinomycin D and daunorubicin were the most potent drugs. When adjusting the drug efficiency for theoretical effect on benign cell isolates and for the varying proportion of tumor cells we observed better correlations with pemetrexed, cisplatin and survival time. Proportion of malignant cells, reactivity to RRM1 and general drug sensitivity correlated to each other and to survival of the patients.

The drug sensitivity in malignant mesotheliomas is highly variable. These results indicate that in vitro testing of drug sensitivity may provide a tool for personalized treatment options.