In vivo evaluation of new therapeutic approaches for the treatment of Small Cell Lung Cancer (SCLC)

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Introduction Small cell lung cancer (SCLC) is characterised by an aggressive clinical course with invariable resistance to chemotherapy despite initially high response rates. There has been little improvement in outcome over the past few decades, with no breakthrough yet in targeted therapies. Thus, the purpose of this study was to evaluate in vitro cytotoxic effects and in vivo antitumour activities produced by different chemotherapy regimens. In particular, our approaches was based on more frequent and low-dose drug administrations compared with conventional chemotherapy, in order to improve efficacy and minimize toxicity.
Several studies on breast cancer showed that significantly lower doses given more frequently on a prolonged schedule proved to be far more effective, including complete tumor regressions, even in mice that were resistant to the same drug when used in a standard MTD regimen.
Methods First, we tested the chemotherapy compounds *in vitro.* ATPlite assay on human SCLC cell lines was used to evaluate cell-growth in response to treatments. The antitumour effect was then investigated in our bioluminescent xenograft ectopic model of small cell lung cancer: this mouse model has been created by inoculation of human SCLC cell line (H69). The tumor onset and progression were evaluated with a bioluminescence imaging (BLI) technique based on luciferase reporter gene. In this regard, before being grafted in mouse lung, the tumor cells were transfected to permanently express luciferase gene.
Results We tested the antitumor efficacy of chemotherapy (carboplatin in particular) at different doses administered every 48h for 21 days. The ectopic subcutaneous model responded very well to treatment with carboplatin, allowing us to accurately monitor tumor progression and therapy response. The maximum dose leads to the disappearance of the mass, but being a dosage evidently toxic, causes the death of the animal during the treatment window. Decreasing concentrations determine a linear increase of the tumor mass, as well as to a visible improvement in the health of the animal. The analysis of the tumor mass confirmed the data extrapolated from in vivo bioluminescence. It is evident that lower concentrations lead to a considerable reduction of the tumor mass in three weeks, on the other hand these animals already from the second week of treatment were visibly less reactive. Since the lowest concentration still causes a considerable reduction compared to saline-treated mice, showing a healthy state almost identical to the untreated ones, may be chosen for setting up combination regimens.
Conclusions These preclinical results indicate a promising activity of this new regimen strategy (frequent and low-dose administration) for the treatment of SCLC, that should be deeper evaluated as monotherapy and as multi-therapy.

References

Romiti A. et al. (2013) - Cancer Chemother Pharmacol. 2013 Mar 9.
Joshi M. et al. (2013) - Adv Exp Med Biol. 2013;779:385-404.
Hong-Yang Lue t al. (2013) - Oncol Lett. 2013 January; 5(1): 3–11.
Puglisi M et al.(2010) - British Journal of Cancer 102, 629–638
Phillips C et al. (2006) - NCI Cancer Bullettin Volume 3 / Number 26
Ruxana T et al.(2005) - Proc Am Thorac Soc; 2(6): 537–540.