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In vivo pharmacokinetics of [11C]docetaxel in lung cancer patients

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Background: Although docetaxel is an effective drug for the treatment of lung cancer, a number of patients does not benefit from this therapy due to tumour resistance. Positron emission tomography (PET) is a non-invasive imaging technique that allows for quantification of radiolabelled docetaxel ([^{11}C]docetaxel) kinetics in tumours and might be useful for predicting tumour response to docetaxel treatment. The aim of the present study was to determine the feasibility and reproducibility of [^{11}C]docetaxel PET scans in lung cancer and to investigate whether [^{11}C]docetaxel uptake was related to tumour perfusion.
Patients and Methods: Twenty-five patients with advanced lung cancer underwent a dynamic PET-CT scan with [^{11}C]docetaxel (60 min) and $H_2{}^{15}O$ (10 min). In addition, 8 patients underwent a second [^{11}C]docetaxel PET scan to assess test-retest reproducibility. Arterial and venous blood samples were collected to measure blood and plasma radioactivity concentrations and to assess the presence of radiolabelled metabolites. Lesions were delineated on the CT scan and projected onto the dynamic PET frames. [^{11}C]docetaxel uptake in tumours was quantified using the Patlak method, giving the net influx rate (K_i). Tumour perfusion was quantified by applying the standard single tissue compartment model to the $H_2{}^{15}O$ data.
Results: Clearance of [^{11}C]docetaxel from plasma was rapid and later PET frames suffered from high liver uptake. Therefore, only the first 10 min of data were used for further analysis. In total, 47 lesions were defined, including both primary tumours and metastases. The median net influx rate of [^{11}C]docetaxel was 0.0103 min^{-1} (range 0.0023–0.0358 min^{-1}). Test-retest [^{11}C]docetaxel PET scans showed good reproducibility with an intraclass correlation coefficient of 0.95. The inter-individual and intra-individual variability of [^{11}C]docetaxel uptake in lung cancer was high. [^{11}C]docetaxel uptake was not associated with tumour size, but correlated with tumour perfusion (Spearman's $\rho = 0.846$, $p < 0.001$).
Conclusions: Measurement of [^{11}C]docetaxel uptake in lung cancer is feasible with good reproducibility. [^{11}C]docetaxel uptake depends on tumour perfusion. The variability of [^{11}C]docetaxel uptake in lung cancer may reflect differential sensitivity to docetaxel treatment, suggesting that PET scans with [^{11}C]docetaxel may be useful for personalized treatment planning.

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Berubicin, a novel mechanistically altered anthracycline potently inhibits cell growth and induces apoptosis in mantle cell lymphoma

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Background: Patients with mantle cell lymphoma (MCL) inevitably relapse despite initial effective therapies, and the disease eventually becomes resistant to the currently existing drugs. Therefore, novel anticancer agents are urgently needed for MCL. Doxorubicin (DOX), an anthracycline, topoisomerase II poison, has demonstrated clinical usefulness in MCL; however, its efficacy is limited by drug resistance. To overcome these limitations, we tested berubicin (BRN), a clinically evaluated representative of a novel class of mechanistically altered anthracycline analogs, as a single agent to treat MCL in vitro.
Materials and Methods: We compared the effects of BRN with DOX and another clinically used agent bortezomib. Four human MCL cell lines, Mino, JeKo-1, SP53, and Granta 519, and fresh primary tumor cells isolated from patients with MCL were treated with BRN, DOX, and bortezomib. The effects of these compounds on cell proliferation, apoptosis, and the cell cycle were analyzed using ^{3}H-thymidine incorporation assay, MTS assay, flow cytometry, and Western blot analysis.
Results: BRN potently inhibited the growth of the established MCL cell lines, as well as the fresh primary tumor cells isolated from patients with MCL in a dose-dependent manner. BRN also potently induced caspase 3−mediated apoptosis in both the established and primary CD20^{+} MCL cells in a dose-dependent manner. Notably, BRN induced G2/M cell cycle arrest in all MCL cell lines tested. BRN was significantly and consistently more potent as a cell growth inhibitor and inducer of apoptosis in MCL than either DOX or bortezomib. Most remarkably, BRN did not inhibit cell growth or induce apoptosis in normal resting bone marrow-derived mononuclear cells at the concentrations that were lethal to MCL cells.
Conclusions: BRN, a novel, mechanistically altered, and clinically evaluated DOX analog that targets topoisomerase II, blocks the transcriptional activity of HIF-1a, and circumvents ABC transporter-mediated efflux, appears to be a promising new agent against MCL that could replace DOX as single agent and/or be used in combination with other drugs.

Apoptosis, necrosis, autophagy

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Induction of acute apoptosis by cisplatin is not associated with damage to nuclear DNA and is likely to be an "off-target effect"

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Apoptosis has been widely proposed as a major mechanism of the anti-proliferative effects of cisplatin and this compound is widely used in experimental studies on DNA damage-induced apoptosis. A problem with these studies is that cisplatin concentrations that are at least one order of magnitude higher than the IC50 (i.e. 20−100 μM) are used to induce apoptosis in short-term experiments (24−48 hr). We find that at these concentrations, cisplatin induces formation of cellular superoxide and that apoptosis is inhibited by superoxide scavengers. Importantly, cisplatin induces caspase activation in enucleated cells (cytoplasts) with the same concentration limits as observed with intact cells − showing that cisplatin-induced apoptosis occurs independently of nuclear DNA damage. Even when cisplatin is used at high concentrations, caspase-3 activation is restricted to the peripheral cell layer of multicellular spheroids, showing that apoptosis is likely not an important outcome in 3-D tumor tissue. At IC50 doses, the antiproliferative effects of cisplatin involve premature senescence and secondary, nonstress-induced apoptosis. We propose that the high cisplatin doses currently used in *in vitro* studies are unphysiological and lead to acute, stress-induced apoptosis that is largely DNA damage-independent and represents an "off-target" effect.
Mandicet al., *J Biol Chem.* 278, 9100−6; Berndtssonet al., *Int J Cancer,* 120:175–180; Fayad et al., *IntJ Cancer* 125, 2450–2455.

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Tumor necrosis factor and CCR5 gene associations with cancer risk

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Genetic polymorphisms of cytokine encoding genes are known to predispose to malignant disease. The cytokine *TNF-α* is a central mediator of inflammation and apoptosis and may possess both pro-tumor and anti-tumor activities. *CCR5*, are believed to play a role in anti-tumor immunity through immune-cell recruitment. It has been suggested from earlier reports that the *TNF-α* can also influence the expression of chemokine receptors and causes *CCR5* down-modulation. It has also been reported that *TNF-α* decreases the *CCR5* expression in peripheral blood monocytes and alveolar macrophages by the production of *RANTES*. The objective of this study was to investigate whether single nucleotide polymorphisms with known functional significance in the genes that are involved in immunoregulatory functions such as, *CCR5, TNF-α* are associated with susceptibility to malignant disease.
In this study, *CCR5Δ32* deletion and polymorphism in the promoter region (position −308) in *TNF-α* gene were determined using polymerase chain reaction-(PCR) restriction fragment length polymorphism (RFLP) methods in patients with cancer and healthy controls. We compared the allelic distribution of these genes adjusted for age and sex between cancer patients and healthy subjects to study the possible association with susceptibility to disease. We also assessed potential interactions between these polymorphisms and different types of cancers.
We report two important findings (1) *TNF 2* allele as genetic risk factor for cancer showing strong association with a significance of $p > 0.00232$ (including all cases typed for *CCR5* mutation) and (2) The significance of *TNF-α* is observed only in the presence of functioning *CCR5* (wild type) with $p > 0.0008$, but not in carriers (deletion) $p > 0.547$ indicating a possible gene interaction involved in immunoregulatory function. In conclusion, our data suggest an important role for *TNF-α* and *CCR5* polymorphisms in cancer. The present findings suggest that the inflammatory process may constitute an important step in the initiation and promotion of solid tumors/cancer. To better understand the interaction of these genes