However, both compounds were able to interfere with the NER process as shown by attenuated repair of UV-induced DNA lesions that are specific NER substrates. Accordingly, combinations of PM01183 and cisplatin were at least additive toward both parental and cisplatin-resistant ovarian cancer cells.
Conclusion: We here show that PM01183 and trabectedin are not repaired by NER, but are able to interfere with the NER process, probably by acting as decoys for NER proteins. Cells with acquired resistance to cisplatin and oxaliplatin show unchanged or even increased sensitivity to the two ETs. Combinations of PM01183 and cisplatin are at least additive toward both parental and cisplatin-resistant ovarian carcinoma cells. Our data provide a mechanistic basis to support clinical trials of PM01183 in combination with cisplatin toward both platinum-sensitive and -resistant tumors.
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523 POSTER

The XRCC1 Arg280His polymorphism is associated with high-grade radiation-induced late toxicity in prostate cancer patients

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Background: Polymorphisms in genes responsible for DNA damage signaling and repair might modulate DNA repair capacity and therefore affect cell and tissue response to radiation and influence individual radiosensitivity. The purpose of the present investigation was to evaluate the role of single nucleotide polymorphisms in genes involved in DNA repair for the development of radiation-induced late side effects in prostate cancer patients treated with radiotherapy.
Patients and Methods: To analyze the role of polymorphisms in DNA repair genes for late toxicity 603 participants from the Austrian PROCAGENE study were included in the present investigation. Eligible for inclusion in the present analysis were male patients with histologically confirmed prostate cancers who underwent three-dimensional conformal radiation therapy. High energy photons (18 MV) were generally delivered in a three-field technique using an anterior and two lateral fields. All patients underwent three-dimensional conformal radiotherapy. Six functional candidate polymorphisms in XRCC1 (Arg194Trp, Arg280His, Arg399Gln), XRCC3 (Thr241Met) and ERCC2 (Asp312Asn, Lys751Gln) were selected and determined by 5′-nuclease (TaqMan) assays.
Results: Within a median follow-up time of 35 months, 91 patients (15.7%) developed high-grade late toxicities (defined as genitourinary and/or gastrointestinal late toxicity RTOG $\geqslant$2). In a Kaplan–Meier analysis, carriers of the XRCC1 Arg280His polymorphism were at decreased risk of high-grade late toxicity ($p = 0.022$). Univariate Cox proportional hazard analyses showed a lower risk of high-grade late toxicity for carriers of the XRCC1 280His allele (HR = 0.28, 95% CI 0.09–0.90; $p = 0.032$), in multivariate analysis the XRCC1 Arg280His polymorphism remained a significant predictor for high-grade late toxicity (HR = 0.27, 95% CI 0.09–0.86; $p = 0.025$). No significant associations were found for the remaining polymorphisms.
Conclusion: We conclude that the XRCC1 Arg280His polymorphism may be protective against the development of high-grade late toxicity after radiotherapy in prostate cancer patients.

524 POSTER

Potent DNA alkylating agents against human prostate cancer in xenograft model

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Prostate cancer is the most common type of cancer in men in the United States. It is the second leading cause of cancer death in U.S. men after lung cancer. The treatment of this disease includes radiotherapy, proton therapy, chemotherapy, immunotherapy and hormone therapy. The cancer cells may metastasize to other parts of body (such as bones, lymph nodes, rectum, and bladder). We have recently designed and synthesized a series of water-soluble phenyl N-mustards by linking phenyl N-mustard pharmacophore to water-soluble benzenes via a urea linker. These compounds possess potent cytotoxicity in vitro and significant therapeutic efficacy in animal model against various human tumor xenografs. Among these compounds, we found that BO-1055 exhibited potent antitumor activity against human prostate cancer in xenograft model. Human prostatic adenocarcinoma cell lines (LNCaP, 22RV-1 and PC-3 cell lines) were used for evaluating the antitumor activity of the newly synthesized compounds. Significant tumor inhibition (>99%) was achieved when nude mice bearing human prostate adenocarcinoma PC-3 (subcutaneous implantation) were treated with BO-1055 [30 mg/kg, Q2D$\times$4 and then 40 mg/kg, Q2D$\times$3, intravenous injection (iv inj.)]. Moreover, we found that this agent possessed potent therapeutic efficacy in nude mice bearing prostate adenocarcinoma 22RV-1 (derived from a human prostatic carcinoma xenograft, CWR22R, an androgen-responsive human PC cell line) via orthotopic implantation. We have also investigated the mechanism of action of BO-1055 and found that this compound is able to induce DNA interstrand cross-linking. This suggests that DNA cross-linking is probably the main mechanism of action of this compound. The early ADME study reveals this derivative is stable in rat plasma with long half-life in rat. The current studies suggest that this agent may have high potential for clinical application.

Gene therapy and antisense approaches

525 POSTER

Design and synthesis of N10-protected pyrrolobenzodiazepine (PBD) prodrugs for use in nitroreductase-mediated GDEPT therapies

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The over-expression of telomerase in cancer cells has been previously exploited for gene therapy strategies. One approach involves the use of a plasmid containing a telomerase promoter to control the expression of an exogenous nitroreductase enzyme capable of activating bioreductively-sensitive prodrugs. CB1954 is the most commonly studied prodrug for use in bioreductive GDEPT approaches, although it has a number of drawbacks including relatively low potency, inherent toxicities and a lack of patent protection. Therefore, we have designed some novel bioreductive prodrugs based on the sequence-selective DNA-interactive pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) antitumour agents.
The PBDs interact covalently with DNA through formation of a covalent aminal bond between their electrophilic N10-C11 position and the nucleophilic C2-NH_2 of guanine bases. The prodrug design concept involves the introduction of a bulky bioreductively-sensitive protecting group at the N10-position which effectively blocks interaction with DNA thus reducing potency. However, release of the N10-protecting group under bioreductive conditions restores the ability to interact with DNA along with the original biological activity.

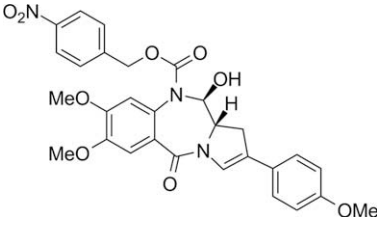

Figure 1: Structure of Nitroreductase PBD Prodrug

As proof-of-principle, we installed a *p*-nitrobenzylcarbamate group at the N10-position of a PBD (Figure 1). We found that upon reduction to the N10-(*p*-aminobenzylcarbamate), this grouping self-immolated to afford the biologically-active parent PBD, *p*-nitrobenzyl alcohol and carbon dioxide. Control molecules including non-reducible N10-benzyl- and N10-SEM-protected analogues incapable of self-immolation were also synthesized. Along with the parent N10-unsubstituted PBD, these molecules were all evaluated in matched *in vitro* panels of A2780 (ovarian), A549 (lung), C33a (cervical) and 5637 (bladder) human tumour cells, one panel being transfected with plasmids containing the Nitroreductase (NTR) gene under the control of a CMV promoter ("NTR+"), a surrogate for the telomerase promoter. The CMV NTR+ panel was found to be more sensitive to the prodrug than the non-CMV NTR panel, with an order of sensitisation of 18.4 > 8.1 > 2.6 and 1.5 for the A2780, A549, C33a and 5637 cell lines, respectively. Crucially, the prodrug was significantly less cytotoxic in all cell lines (*e.g.,* IC_{50} = 0.29 and 0.015 μM in NTR+ and NTR- A2780 cells, respectively) compared to the parent non-N10-substituted PBD (*e.g.,* IC_{50} = 0.000151 μM and 0.00028 μM in NTR+ and NTR- A2780 cells, respectively). Thus, in A2780 NTR+ cells, the prodrug is 1,920-times less