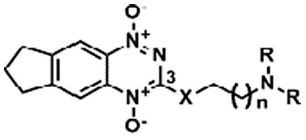
(AUC_p) and the in vivo hypoxic selectivity (HCD). TTOs with favourable predictions of EVT, AUCp and HCD were tested in vivo.
Maximum tolerated doses (MTD) given i.p. were determined in CD-1 nu/nu mice and plasma PK parameters (AUC, C_{max}) measured at 75% of the MTD. Lipophilic TTOs with strongly basic amine sidechains were found to be considerably more toxic in vivo, and had lower AUC values, than moderately lipophilic TTOs with weakly basic side chains. TTOs with favourable PK parameters were assessed for anti-tumour activity in combination with radiation by excision assay of HT29 xenografts 18 h after treatment. Administration of the lead compound, SN30000 at 75% of MTD, 5 min after RAD, gave an additional 1.4 logs of cell kill above RAD alone, compared with TPZ (0.6 additional logs).
The combination of IC_{50} and HCR with PK/PD modelling successfully identified a novel TTO, SN30000, with improved in vivo activity compared to TPZ.



X = NH, CH_2; n = 1,2

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Substituted nitro(chloromethyl)benzindolines (nitroCBIs): a new class of hypoxia selective cytotoxins with in vivo activity

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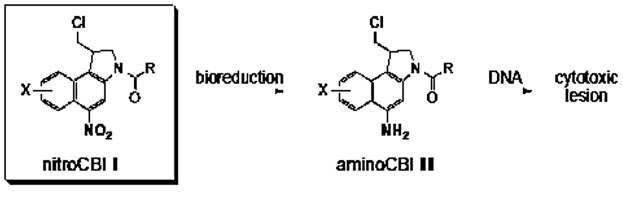
Amino(chloromethyl)benzindolines (aminoCBIs, **II**) are DNA alkylating agents related to the natural products CC-1065 and the duocarmycins. They share many of the same properties (sequence selective alkylation at N3 of adenine, high cytotoxic potency) but in addition are amenable to the preparation of hydrolytically stable prodrug forms. Here we describe the potential of nitro(chloromethyl)benzindolines (nitroCBIs, **I**) to act as prodrugs activated by bioreduction in hypoxic regions of tumours.



R = minor groove binding side chain; X = H, electron withdrawing group

We show that (a) nitroCBIs **I** are considerably less toxic than aminoCBIs **II** under aerobic conditions in vitro, (b) **I** are metabolised to **II** selectively under hypoxic conditions, (c) several nitroCBIs **I** provide hypoxic cytotoxicity ratios (HCRs) of over 100-fold in vitro, and (d) alcohol-substituted nitroCBIs **I** can be converted to water soluble phosphate pre-prodrugs. A lead compound, SN29730, can be formulated in PBS containing $NaHCO_3$ (soluble at 25 mM), is well tolerated (MTD 100 micromol/kg iv in CD1 mice), has favourable pharmacokinetic properties (phosphate rapidly hydrolysed to corresponding alcohol), and is active in vivo as a single treatment but also in combination with radiation in human cervical carcinoma xenografts. In SiHa xenografts in combination with 15 Gy whole body irradiation SN29730 reduces the number of viable clonogens per gram of tumour tissue by over 4 orders of magnitude (radiation alone provides less than 2 logs of cell kill) at doses well below the MTD. These properties strongly suggest that nitroCBIs have potential for development as a new class of hypoxia selective cytotoxins.

260 POSTER

SN 30000: a tricyclic triazine 1,4-dioxide hypoxia-selective bioreductive drug with superior in vivo activity to tirapazamine

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Tirapazamine (TPZ) is a hypoxia-selective bioreductive drug that has showed promising clinical activity in combination with chemo-radiotherapy. However, the activity of TPZ is limited by poor extravascular transport (EVT) restricting diffusion to the target hypoxic regions in tumours and high toxicity limiting the number of doses that can be administered.
We have developed a novel series of tricyclic triazine 1,4-dioxides (TTOs) with improved EVT relative to TPZ. Certain moderately lipophilic TTOs with weakly basic sidechains provided favourable plasma PK while having greater hypoxic potency and hypoxic selectivity than TPZ across a panel of human tumour cell lines.
Antitumour activity was assessed by excision assay of HT29 xenografts 18 hr after treatment. Mice were treated with drug alone (75% of MTD) ± radiation (RAD, 20 Gy whole body). RAD alone gave 1.9 logs cell kill while the TTOs (administered 5 min after RAD) gave up to an additional 1.4 logs kill, compared with TPZ (0.6 logs). The activity of SN 30000, the most active TTO in the HT29 assay, was confirmed in SiHa cervix carcinoma xenografts. Administration of SN 30000 (0.56 mmol/kg) from 2 hr before to 5 min after RAD (15 Gy) provided 1.3−2.9 logs kill in addition to RAD alone. The greatest activity was obtained when SN 30000 was administered 1 hr before RAD. In contrast, TPZ (0.13 mmol/kg) showed no significant time dependence, with lower activity at all times (maximum of 0.8 logs kill in addition to RAD).
Bidaily dosing with SN 30000 provided an MTD of 0.24 mmol/kg/dose over 4 days, allowing administration of a total dose 2.5-fold higher than the single dose MTD. The activity of SN 30000 in combination with fractionated RAD (8 ×–2.5 Gy) was determined by excision assay of HT29 and SiHa xenografts. With fractionated dosing there was no time dependence for administration of either SN 30000 or TPZ (8 × 0.08 mmol/kg) from 1 hr before to 5 min after each RAD dose in SiHa or HT29 xenografts. At all times greater cell killing (up to 2.2 logs in addition to RAD only) was obtained for SN 30000 than for TPZ (up to 1.0 logs in addition to RAD). The increased *in vivo* activity of SN 30000 relative to TPZ was achieved with no increase in host toxicity (weight loss, histopathology of normal tissues). Thus SN 30000 has a higher therapeutic ratio than TPZ as a hypoxic cytotoxin in two human tumour xenograft models.

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Banoxantrone (AQ4N), a tissue CYP 450 targeted prodrug: the results of a Phase I study using an accelerated dose escalation in patients with advanced solid tumors

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Background: AQ4N was rationally designed to have anti-tumor activity following bioreduction by tissue cytochrome P450 to AQ4, an active DNA topoisomerase II inhibitor. Preclinical studies demonstrated AQ4N selectively targets lymphoid tissues and hypoxic tumor tissues. This study assessed the maximum tolerated dose (MTD), pharmacokinetic (PK), and pharmacodynamic (PD) of repeated weekly dosing of AQ4N in patients (pts) with advanced cancers.
Methods: AQ4N was administered IV on Days 1, 8, and 15 of a 28-day cycle in the following dose cohorts: 12, 24, 48, 96, 192, 384, 768, and 1200 mg/m^2. Accelerated titration design 2B was employed and the MTD was defined by ⩽ 33% of 6 pts with a drug-related dose limiting toxicity (DLT). Response was assessed every 8 weeks by RECIST.
Results: 16 pts were enrolled. A single pt per cohort was treated up to 384 mg/m^2. At 1200 mg/m^2, 2 of 5 pts experienced a DLT (Grade 5 respiratory distress and Grade 3 fatigue). A total of 5 pts were treated without toxicity at the 768 mg/m^2, and established this dose as MTD. One pt in the 1200 mg/m^2 cohort died during the trial from acute complications of metastatic soft tissue sarcoma and respiratory distress. The most common related adverse events (AE) observed were skin discoloration (81%), chromaturia (75%), fatigue (38%), nausea (28%), vomiting (25%), and diarrhea (25%). 7 pts experienced 8 serious AEs. One pt (48 mg/m^2) with renal cancer has had stable disease for > 20 months. The PK was linear over all doses studied and no accumulation was observed after repeated doses. At 768 mg/m^2 (n = 4), the Day 1 AQ4N C_{max} was 99.8±27.0 μg/mL, AUC $_{0-\infty}$ was 259.5±67.8 μg h/mL, and $T_{1/2}$ was 3.9±0.7 h (range 3.1−4.8 h). Multiple cycles of AQ4N at weekly doses of 768 mg/m^2 or higher demonstrated a mild reduction of both lymphocyte count and ANC.
Conclusions: AQ4N is well-tolerated when administered on a weekly schedule. AQ4N levels sufficient for anti-neoplastic activity in pre-clinical models are achieved with weekly dosing at 768 mg/m^2. AQ4N monotherapy and combination trials with chemo- and radiation therapy are planned.