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Pediatric Preclinical Testing Program (PPTP) evaluation of the anti-CD19-DM4 conjugated antibody SAR3419

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Background: SAR3419 is composed of the humanized anti-CD19 antibody huB4 conjugated with the potent cytotoxic maytansinoid, DM4, a tubulin polymerization inhibitor. SAR3419 has shown preclinical in vivo activity against human B-cell lymphomas, and was selected for evaluation against the Pediatric Preclinical Testing Program (PPTP) in vitro and in vivo panels of B-lineage acute lymphoblastic leukemia (ALL), which express high levels of cell surface CD19.
Methods: The PPTP includes a molecularly characterized in vitro panel of leukemia cell lines (n = 7) and in vivo panel of ALL xenografts (n = 10), representing the common subtypes of pediatric ALL. SAR3419 was tested in vitro against the RS4;11 (CD19+) and MV4;11 (CD19−) cell lines at concentrations from 0.01 nM to 10 nM, and against the PPTP in vivo panel (n = 6) at a dose of 10 mg/kg administered weekly $\times 3$ via intraperitoneal injection to NOD/SCID mice. Three measures of antileukemic activity were used: (1) response criteria modeled after the clinical setting; (2) treated to control (T/C) proportion of human CD45+ cells in the murine peripheral blood (%huCD45+) at day 21; and (3) a time to event (25% huCD45+ cells) measure based on the median EFS of treated and control lines (intermediate activity required EFS T/C >2, and high activity additionally required a net reduction in the %huCD45+ cells at the end of the experiment).
Results: SAR3419 was ineffective against MV4;11 cells, but potently killed the RS4;11 cell line with IC50.

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Preclinical evaluation of the marine compound PM00104 within the ITCC pediatric tumor cell line panel in vitro and in vivo

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Background: The European consortium Innovative Therapies for Children with Cancer (ITCC) aims to develop new anticancer agents for the treatment of pediatric malignancies. The ITCC is composed of 35 clinical pediatric oncology centres and 9 laboratories for preclinical evaluation in six European countries. PM00104 (Zalypsis®) PM00104 is a new synthetic alkaloid related to Jorumycin and the Renieramycins with in vitro growth-inhibitory properties in the low nanomolar range as well as anti-tumor activity in vivo against several adult cancers. PM00104 affects cell cycle, displays DNA binding properties and transcriptional inhibition. PM00104 is being evaluated in 4 phase I clinical trials with different schedules.
Methods: In vitro cytotoxicity of PM00104 was screened by MTS-assay on a panel of 24 pediatric tumor cell lines (CL), composed of 4 CL of the following tumor types: Ewing sarcoma, acute lymphatic leukemia, medulloblastoma, neuroblastoma, osteosarcoma, and rhabdomyosarcoma. Cells were exposed for 72 h to PM00104 at 1.4 fmol/L to 14 nmol/L. Experiments were performed in triplicate. GI50 was considered as proof of growth inhibition and LC50 represents cytotoxicity. Anti-tumor activity was evaluated against an advanced subcutaneous rhabdomyosarcoma xenograft model in athymic mice.
Results: PM00104 significantly reduced growth of all CL in a dose dependent manner. The most sensitive CL in terms of growth inhibition were within the group of neuroblastoma, rhabdomyosarcoma and ALL with GI50s below 1 nmol/L (0.5–1.0) for 2, 3 and 2 out of 4 CL respectively. The mean$\pm$SD LC50 values were 14.0$\pm$8.1 nmol/L in Ewing sarcoma, 9.0$\pm$5.9 nmol/L in ALL, 15.5$\pm$12.7 nmol/L in medulloblastoma, 7.3$\pm$6.5 nmol/L in neuroblastoma, 13.2$\pm$2.3 nmol/L in osteosarcoma and 13.1$\pm$14.3 nmol/L in rhabdomyosarcoma, respectively. In RD rhabdomyosarcoma xenografts, PM00104 administered i.v. at 0.8 and 1.0 mg/kg q7dx4 resulted in 100% tumor regression (7 complete and 1 partial/8 tumors and 9/9 complete, respectively) and significant tumor growth delay in time to reach 5 times initial tumor volume of 38.3 and 41.7 days compared to controls ($p < 0.001$; Kruskal Wallis test).
Conclusions: PM00104 exhibits cytotoxic activity against most pediatric CL in vitro, particularly neuroblastoma, ALL and rhabdomyosarcomas, and significant anti-tumor activity against rhabdomyosarcoma xenograft model.

Phamacogenomics

194 POSTER

How to prescribe standard chemotherapy or targeted-therapy using a fully featured relational database

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Background: Treatments in oncology should be ordered using relational database management systems (RDBMS). This is very useful in both standard clinical practice and clinical trials. Electronic prescribing and computerized drug management can improve the safety, quality and cost-effectiveness of prescribing.
Material and Methods: This module was constructed using a RDBMS as FileMaker Pro™ (FileMaker Inc, Santa Clara, CA, USA). It has two different parts: the input and the output section. (a) Variables that are included as "input": gender, weight, height, anatomic location of cancer, protocol of treatment, number of cycle, performance status (ECOG), creatinine, presence of anxiety, alcohol abuse, pain intensity (visual analogic scale), date of start of the actual chemotherapy and the previous cycle, area under the curve (for carboplatin). (b) Variables that are calculated as the "output": age, body surface area (du Bois formula), body mass index, obesity class (the International classification), the theoretical time interval and delay duration between two consecutive cycles of treatment, the score of patient and protocol-related emesis with an associated global emesis category risk (as defined by Grunberg), estimated creatinine clearance rate (Cockcroft-Gault and MDRD formula), categories of renal dysfunction (National Kidney Foundation), dose of carboplatin (Calvert formula), pain category, date of the next cycle, efficiency of dose intensity (DI).

Date 15.07.2007

CHEMOTHERAPY PRESCRIPTION
"If what you are doing good, keep doing it" - Loeb's rules of therapeutics

Time 19:21

First name	Xxx	Identification	5707
Last name	Dddd	Year of file	1998
Sex	female	Age	48 years
Date of birth	12.10.1959	Body surface area (BSA)	1,82 m^2
Weight (kg)	75	Body mass index	27,5 kg/m^2
Height (cm)	165	Cycles interval	28 days
Anatomic location	Breast cancer	Delayed	5 days
Protocol	AVASTIN + PACLITAXEL	Emesis score (patient)	5
Cycle number	2	Emesis risk (patient)	High risk
Creatinine	123 µmol/l	Emesis score (protocol)	2
PS ECOG	1	Emesis (global score)	High risk
Alcohol abuse	○ Yes ◉ No	Clearence of creatinine	58,8 ml/min/m^2
Anxiety	○ Yes ◉ No	Moderate chronic renal insufficiency - stage 3 KDOQI	
Pain grade (VAS)	2	Pain class WHO	Mild pain
Date of start	20.06.2007	Blood group	0 I
Date of previous cycle	18.05.2007	Date of the next cycle	18.07.2007
Oncologist	Banu Eugeniu	Clinical trial	
AUC		*Efficiency of dose intensity*	78 %

Day		Drug	Value		Theoretical	Real dose	Observation	% DI
1	20.06.2007	Bevacizumab	10	mg/kgc	750	700	iv infusion, 90 min	79
1	20.06.2007	Paclitaxel	90	mg/mp	164	150	iv, 3h, in 500 ml SF PVC	78
8	27.06.2007	Paclitaxel	90	mg/mp	164	150	iv, 3h, in 500 ml SF PVC	78
15	04.07.2007	Paclitaxel	90	mg/mp	164	150	iv, 3h, in 500 ml SF PVC	78
15	04.07.2007	Bevacizumab	10	mg/kgc	750	700	iv infusion, 60 min	79

VAS: Visual Analogic Scale PS ECOG: Eastern Oncology Cooperative Group Performance Status WHO: World Health Organisation
National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) Emesis score: Grunberg and col. (*Support Care Cancer 2005*)

Figure 1.