range of biological activity depending on the parent aldehyde or ketone heterocyclic TSCs have aroused considerable interest in chemistry and biology due to their antibacterial, antimalarial, antineoplastic and antiviral activities. In this study we report the toxicity and antitumor activity of new platinum (II) complexes: the TSCs of 2-formyl and 2-acetyl pyridine, containing azepane ring incorporated at N(4) position, HL^1 (**1**) and HL^2 (**2**) with platinum (II) afforded the complexes, [Pt(L^1)Cl] (**3**) and [Pt(L^2)Cl] (**4**).
Material and Methods: Stock solutions of the compounds **1**-**4** were prepared immediately before use. They were suspended in corn oil following initial dissolution in 10% DMSO. BDA/2 mice were used for toxicity studies. Lymphoid leukemia L1210 bearing BDF1 mice were used to determine the antitumor effect. The tumor was maintained in ascetic form by injection of 1×10^5 cells at 7-day intervals intraperitoneally in DBA/2 mice. The antitumor activity of the compounds was assessed from the oncostatic parameter T/C %. Treatments were given as a single LD10 dose on day 1.
Results: The LD10 therapeutic dose was 40, 37, 53 and 76 mg/Kg for compounds **1**-**4**.
The ligands **1** and **2** cause acute toxicity and display some antitumor activity, while the compounds **3** and **4** show reduction of the toxicity and high increase of survival time of drug-treated leukemia bearing mice. The ligand **2** is achieving a T/C % value of 117 and the platinum (II) complex **4**, of 384. The ligand **1**, is achieving a T/C % value of 141, while the platinum (II) complex **3**, of 301. One of six mice of complex **3**-treated animals was cured and was considered as long-term survivor, i.e. mice alive 90 days.
Conclusions: The replacement of a methyl group at position 7 (HL^2) by a C(7) H group (HL^1) in the 2-pyridil position, causes marked differences in the biologic results as significant increase of life-span of the drug-treated leukemia bearing mice (T/C % 141 and 117 for HL^1 and HL^2, respectively). Probably the Pt (II) complexes [Pt(L^1) Cl] (**3**) and [Pt(L^2) Cl] (**4**), may interact easier with DNA or proteins than the other compounds. Complex **4** was proved to be the most potent antileukemic agent, comparing the T/C% value. Compound **3** yielded a high T/C% of 301 and afforded additionally one of six cures. Compounds **3** and **4** had decreased toxicity combined with impressive potency.

1219 POSTER

Trans-resveratrol reverse drug resistance to docetaxel: a preliminary in vivo study

F. Rosso[1], A. Grimaldi[1], A. Barbarisi[1], V. Avvisati[1], M. De Chiaro[2], A. Di Lazzaro[2], C. Arra[3], A. Barbieri[3], G. Palma[3], R.V. Iaffaioli[2]. *[1]Facoltà di Medicina e Chirurgia Seconda Università, Scienze Anestesiologiche Chirurgiche e dell'Emergenza, Napoli, Italy; [2]Istituto Nazionale Tumori "G. Pascale", Dipartimento Entero-Proctologico, Napoli, Italy; [3]Istituto Nazionale Tumori "G. Pascale", Animal Facility, Napoli, Italy*

Background: Chemotherapeutic drug resistance remains a significant obstacle in the control of prostate cancer in particular of the Docetaxel, that represents the major drug in human prostate cancer treatment. Previous "in vitro" studies showed the capacity of trans-resveratrol to reverte drug resistance to docetaxel in human prostate cancer cells (DU-145). Here, we investigate the sensitization effects of trans-resveratrol in xenograft nude mice models to improve the efficacy of this treatment in prostate cancer.
Material and Methods: Docetaxel-resistant human androgen-independent prostate carcinoma cell line **(**DU-145) were developed by cell culture in medium containing Docetaxel in a dose escalation manner (starting from 1 nM until to 10 nM). Docetaxel-resistant DU-145 cells were injected subcutaneously in posterior legs of 5 nude mice (experimental group) at concentration of 1×10^6 cells/100 μL. After tumor establishment, animals received Docetaxel (5 mg/Kg/4 d) trans-resveratrol by Alzet osmotic pumps placed subcutaneously in such a way to reach a constant blood concentration of 10 μg/mL for 1 mounth. Control group (5 nude mice) were treated only with Docetaxel (5 mg/Kg/4 d) subcutaneously. Weekly, tumor growth were monitored by micro-ultrasound in vivo imaging method and levels of tumor angiogenesis were studied by molecular biomarker (VEGFR2).
Results: Docetaxel-resistant human androgen-independent prostate carcinoma cell line **(**DU-145) was successfully implanted in nude mice, developing a xenograft cancer model for the "in vivo" study of Docetaxel drug resistance. Tumor volume measurements by micro-ultrasound method showed that in experimental group a marked and statistically significative regression of tumor evaluated when nude mice were treated with Docetaxel and trans-resveratrol respect to control group treated only with Docetaxel. Moreover, also tumor angiogenesis in experimental group were less marked respect to control group.
Conclusions: Further experiments are necessary for a better evaluation of the combined effect of trans-resveratrol and Docetaxel. However, our data showed that trans-resveratrol was able to revert drug resistance to Docetaxel in a xenograft model, opening the new way to a clinical trials for the combined use in the therapy of human prostate cancer.

1220 POSTER

Antitumor activities of nab-rapamycin (ABI-009) enhanced by combination with kinase inhibitors Erlotinib and Perifosine

O. D'Cruz[1], V. Trieu[1], N. Desai[1]. *[1]Abraxis BioScience, R&D, Los Angeles, USA*

Background: *Nab*-rapamycin (ABI-009) was developed using proprietary *nab*-technology and showed dose-linear pharmacokinetics and safety up to 90 mg/kg in rats. ABI-009 exhibited effective antitumor activity at 40 mg/kg against a panel of human tumor xenografts. The goal of this study was to develop an effective combination regimen for ABI-009 to test the hypothesis that inhibition of mTORC2, in addition to inhibition of mTORC1 by rapamycin, is necessary to achieve complete shutdown of mTOR signaling pathway.
Materials and Methods: Subcutaneous human breast (MDA-MB-231) tumors were grown in athymic nude mice and treated intravenously (IV) with ABI-009 alone at 40 mg/kg (3xwkly/4 wks) and in combination with Erlotinib, Perifosine, Cetuximab, doxorubicin, SAHA, and oxaliplatin.
Results: ABI-009 was highly effective as a single agent against MDA-MB-231 breast tumor xenografts with 75% tumor growth inhibition (TGI). Combination with Erlotinib resulted in TGI of 85% and 95% (50 and 100 mg/kg respectively, daily/4 wks, IP), 92% and 96% for Perifosine (30 and 60 mg/kg respectively, 3×wkly/4 wks, PO), 83% and 87% for Cetuximab (20 and 40 mg/kg respectively, 3×wkly/4 wks, IP), 83% and 90% for doxorubicin (2.5 and 5 mg/kg respectively, wkly/10 wks, IV), 82% and 90% for SAHA (50 mg/kg daily/7 or 14 days respectively, IP), and.82% and 85% for oxaliplatin (5 and 10 mg/kg respectively, wkly/4 wks, IV).
Conclusions: ABI-009 alone was highly effective against MDA-MB-231 human breast tumor xenografts. Antitumor activity of ABI-009 was significantly increased in combination with kinase inhibitors (Erlotinib – EGFR kinase inhibitor, and Perifosine – AKT inhibitor) with both showing significant improvement versus ABI-009 alone. In contrast, combination of ABI-009 with anti-EGFR monoclonal antibody Cetuximab was not effective. Antitumor activity of ABI-009 was significantly increased in combination with doxorubicin – a topoisomerase inhibitor, and SAHA – an HDAC inhibitor, but not in combination with oxaliplatin – a DNA crosslinker. The synergy of these combinations confirmed that rapamycin is active only on TORC1 and that suppression of TORC2 via AKT or PI3K pathways is a means of increasing activity of mTOR inhibitors.

1221 POSTER

Enhanced sensitivity to Bortezomib pro apoptotic effects in human cancer cells with acquired resistance to anti-EGFR TKIs

F. Morgillo[1], F. Cantile[1], M. Fasano[1], T. Troiani[1], E. Martinelli[1], L. Vecchione[1], M. Orditura[1], F. De Vita[1], F. Ciardiello[1]. *[1]Seconda Università degli Studi di Napoli, Medical-Surgical Department, Napoli, Italy*

Background: Despite great clinical promise the majority of cancer patients show either intrinsic resistance or acquired resistance to EGFR inhibitor therapies. Bortezomib (PS-341; Velcade) is an approved drug for the treatment of haematological neoplasms and is being currently evaluated for the treatment of solid cancers. Recent works showed that bortezomib may play a role as sensitizer for the EGFR inhibitor demonstrating a rationale for the combined use of bortezomib with EGFR inhibitors and thus in cancer cells not anymore responding to the EGFR blockade.
Materials: We developed gefitinib- and erlotinib-resistant non small cell lung cancer (Calu 3) and colon cancer (HCT116) cell lines.
Results: These resistant cell line showed iperactivation of Akt and survivin if compared to parental lines. Bortezomib treatment induced a strong inhibition of cell proliferation and inhibition of Akt and survivin and induction of apoptosis, but in addition to the inhibitory effect on Akt signalling, bortezomib showed a strong ability to induce the expression of GADD153, a well-recognized ER stress-inducible transcription factor, and DR5, in all resistant cell lines, but not in wild type cells. Furthermore, bortezomib induced significant PARP and bid cleavage by caspase 8 activation.
Conclusions: Together, these findings support a mechanistic framework for the induction of apoptosis in resistant cells by bortezomib in which the ER stress-inducible transcription factor, GADD153, is induced, leading to up-regulated DR5 expression and stimulation of the extrinsic apoptotic pathway.