(MDR) associated with expression of energy-dependent transport proteins, extruding MDR-drugs out of the cells. In fact, this is an explanation of the well-known clinical phenomenon of increased efficacy of platinum agents in combination with inactive MDR-drugs in treatment of MDR tumors. It is obvious then that to maximize platinum inhibition of MDR-transporter function the sequence of drug administration "platinum-MDR-drug" should be maintained during the entire chemotherapy duration. Our own clinical experience may be a positive example demonstrating efficacy of this approach.
Design of the investigation: Patients with locally-advanced esophageal cancer received preoperative chemotherapy with cisplatin, etoposide, 5-fluorouracil, leukovorin (FLEP); cisplatin being administered by different modes, i.e. by standard schedule: cisplatin on day 1, or by modified schedule: cisplatin on days 1 to 3. The remaining drugs were always given on a daily basis, with etoposide administered after cisplatin. Response was assessed after 2 three-day cycles with a 3-week interval. The 36 patients enrolled in the two arms were fairly homogeneous in terms of major clinical characteristics.
Results: The number of cases demonstrating decreased severity of dysphagia after chemotherapy completion was greater in the modified schedule group (43% vs. 24% of cases), though there were more patients with higher dysphagia intensity in this group at baseline (19% vs. no patients with grade III dysphagia). More patients receiving modified FLEP regimen as compared with the standard regimen group demonstrated decrease (60% vs. 48%) or no change (40% vs. 26%) in disease extent by x-ray after chemotherapy completion. Complete responses (20% of cases) were shown in the modified regimen group only, and no patients had progressive disease vs. 26% of cases with progressive disease in the standard regimen group. And finally, more patients receiving modified FLEP survived 1 year of follow-up (79% vs. 65%).
Conclusion: Although these findings are but interim, we nevertheless believe that modification of cisplatin administration schedule alone may improved response to chemotherapy even in this very serious and a priori resistant patient category.
Supported by Russian Foundation for Basic Research (Grant 07−04–00082).

503 POSTER

ABCG2 transporter gene expression in childhood rhabdomyosarcoma

H.P. McDowell[1], S. Marsilio[2], P. Altavista[3], S. Bosco[4], A. Donfrancesco[5], A. Inserra[6], P.D. Losty[7], C. Dominici[2]. *[1]Royal Liverpool Children's NHS Trust Alder Hey, Oncology, Liverpool, United Kingdom; [2]La Sapienza University, Pediatrics, Rome, Italy; [3]ENEA Research Center Casaccia, Toxicology and Biomedical Sciences, Rome, Italy; [4]La Sapienza University, Experimental Medicine/Pathology, Rome, Italy; [5]Bambino Gesù Children's Hospital, Oncology, Rome, Italy; [6]Bambino Gesù Children's Hospital, Surgery, Rome, Italy; [7]Royal Liverpool Children's NHS Trust Alder Hey, Surgery, Liverpool, United Kingdom*

Background: Multidrug resistance (MDR) to cytotoxic drugs can be caused by increased expression of one or multiple genes belonging to ATP-binding cassette (ABC) superfamily, which function as drug efflux transporters. In childhood rhabdomyosarcoma (RMS), ABCB1 (MDR1) and ABCC1 (MRP1) genes have been shown to be expressed and their role in determining MDR and therapeutic failure has been described. ABCG2 (BCRP) is the third ABC gene primarily related to MDR. This study was aimed at investigating if this gene is expressed in childhood RMS and the possible associations with clinicopathological features.
Materials and Methods: Primary tumor samples were obtained and snap frozen from 26 pts (14 male/12 female), aged 5–183 months (median, 59), with newly diagnosed RMS. Primary site was favourable (orbit and genitourinary non-bladder/prostate) in 5 pts and unfavourable (head and neck parameningeal and non-parameningeal, genitourinary bladder or prostate, extremity and others) in 21. Pts were staged according to the IRS post-surgical grouping system and assigned as group I (n. 2), II (n. 6), III (n. 16) or IV (n. 2). Histological subtype was embryonal in 20 pts and alveolar in 6. ABCG2 mRNA expression in RMS samples, normal skeletal muscle (constitutive low expression) and normal ovary (constitutive high expression) obtained from healthy voluntary donors (5 for each tissue) was measured by quantitative real-time PCR. Institutional written informed consent from the patient's parents and ethical approval according to local institutional guidelines were obtained.
Results: ABCG2 mRNA levels significantly higher than the mean level in normal skeletal muscle were found in all 26 RMSs, with 9/26 (35%) tumors expressing high levels, i.e., levels in the range ($\pm$20%) of the mean level in normal ovary. No associations between ABCG2 mRNA levels and well-established clinicopathological features such as age at diagnosis, sex, primary site, and size of primary were demonstrated. A non significant trend was identified for tumors with high levels of ABCG2 expression to have embryonal histology: 8/20 (40%) of embryonal cases vs. 1/6 (17%) of alveolar cases ($p = 0.7$).
Conclusions: ABCG2 mRNA expression in childhood RMS is widely increased compared to its normal counterpart, with a substantial part of tumors expressing high levels, i.e., levels physiologically significant. The role of ABCG2 in determining MDR in RMS deserves further investigations in a larger series.

Monoclonal antibodies and targeted toxins/nuclides

504 POSTER

GA101, a therapeutic glycoengineered CD20 antibody recognizing a type II epitope mediates outstanding anti-tumor efficacy in Non-Hodgkin lymphoma xenograft models and superior B cell depletion

C. Klein[1], F. Herting[1], T. Friess[1], C. Gerdes[2], A. Nopora[2], S. Bauer[3], R. Grau[2], E. Moessner[2], J. Dal Porto[4], P. Umana[5]. *[1]Roche Diagnostics GmbH, Discovery Oncology, Penzberg, Germany; [2]GLYCART Biotechnology AG, Discovery Oncology, Schlieren, Switzerland; [3]Roche Diagnostics GmbH, Pharma Research, Penzberg, Germany; [4]Roche Palo Alto, Inflammation Discovery, Palo Alto, CA, USA; [5]GLYCART Biotecnology GmbH, Discovery Oncology, Schlieren, Switzerland*

Background: GA101 is the first humanized, glycoengineered CD20 antibody recognizing a type II epitope. GA101 was derived by humanization of the murine B-Ly1 antibody and is characterized by high binding affinity, type II mode of CD20 binding with reduced CDC but strong direct cell death induction compared to classical type I CD20 antibodies. The glycoengineered Fc region binds with enhanced affinity to FcgRIIIa on immune effector cells leading to enhanced ADCC.
Material and Methods: We studied the dose-dependent effects of GA101 on the growth of s.c. and orthotopic NHL xenografts in SCID beige mice; both as single agent and in combination with chemotherapeutic agents and Bcl-2 inhibitors in direct comparison to rituximab. Depletion of non-malignant B cells was studied in hCD20 transgenic mice and in cynomolgus monkeys.
Results: In various NHL models GA101 demonstrated outstanding anti-tumor efficacy. Specifically, complete tumor remission was induced in SU-DHL4 DLBCL xenografts. By contrast, rituximab at equal or higher doses was only able to slow down tumor progression. Treatment with GA101 increased the median and overall survival in an orthotopic disseminated Z138 MCL model compared to rituximab. Combination studies showed that GA101 works in a synergistic and superior manner in combination with chemotherapeutic agents such as vincristine or cyclophosphamide as well as with novel targeted therapeutic agents such as Bcl2 inhibitors. In hCD20 transgenic mice, GA101 demonstrated superior depth of B cell depletion. The increased B cell depletion extended into the peripheral lymphoid compartments and to the range of B cell subsets targeted. Analogous findings were observed in cynomolgus monkeys where the efficacy of GA101 in depleting B cells in lymphoid tissues was compared with that of non-glycoengineered GA101 and rituximab. These studies showed that the enhanced anti-tumor efficacy and depth of depletion observed with GA101 treatment is influenced by its unique binding mode and the induction of CD20-dependent cell death.
Conclusions: In summary, the data demonstrate that GA101 represents a novel class of CD20 antibodies with outstanding efficacy compared to classical type I CD20 antibodies. GA101 is currently in Ph I clinical trials. It is anticipated that the combination of the type II epitope recognition with improved ADCC potency exclusive to GA101 will translate into superior clinical efficacy establishing GA101 as best in class anti-CD20 therapy.

505 POSTER

Preliminary results of a phase II clinical trial of the anti EGFR monoclonal antibody Nimotuzumab in combination with whole brain radiation therapy in patients diagnosed with advanced non-small cell lung cancer tumors unresectable brain metastases

A. Macias[1], E. Neninger[2], E. Santiesteban[3], J. Figueredo[4], A. Hernandez[4], F. Aguirre[5], N. Aguilera[6], T. Crombet[1]. *[1]Center of Molecular Immunology, Clinical Immunology, C. Havana, Cuba; [2]Hermanos Almejeiras Hospital, Oncology Unit, C. Havana, Cuba; [3]University Hospital J R Tabranes, Oncology Unit, Matanzas, Cuba; [4]Clinical-Surgery Investigacional Center Hospital, Neurosurgery Unit, C. Havana, Cuba; [5]University Hospital JR Tabranes, Oncology Unit, Matanzas, Cuba; [6]National Clinical Trial Coordinator Center, Clinical Trial Unit, C. Havana, Cuba*

Brain metastases are the most common intracranial tumor of adults. Lung cancer is the main primary tumor given rise to brain metastases.