

In multivariate analysis of OS performed by stage, age, MNA, 1p, 9p deletions and 17q gain as covariates patients with stage IV (hazard ratio (HR) 2.561 95% CI 1.034–6.346, $p=0.042$), MNA (HR 2.494 95% CI 1.005–6.189, $p=0.049$) and 9p deletion (HR 3.054 95% CI 1.046–8.917, $p=0.041$) had significantly poor survival.

Investigation of CNVs in relapsed NB samples revealed appearance of new alterations in 9 cases, stable spectrum of aberrations in 3 and lack of CNVs in 5. Patients harboring new CNVs had significantly worse survival after relapse comparing with those who had identical CNVs or lack of CNVs in recurrence: EFS 0.00, OS 0.14 ± 0.13 vs both 0.73 ± 0.16 , $p=0.014$, $p=0.045$.

Conclusions: CNVs have prognostic significance in primary and relapsed NB. This fact encourages perform tissue or liquid biopsies in cases of the tumor recurrence.

No conflict of interest.

1401

ORAL

Metronomic topotecan causes a favorable type of therapy-induced-senescence and prolongs survival in MYCN amplified neuroblastoma xenografts

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Background: Cancer therapy with high-dose DNA-damage inducing drugs causes senescence, a cellular stress response, leading to cell cycle exit and the formation of a typical senescence associated secretory phenotype (SASP). While some components of the senescence secretome reinforce growth-arrest and act immune-stimulatory, others are tumor-promoting. Here we aimed at evaluating whether metronomic, i.e. long-term, repetitive low-dose, drug treatment will induce senescence in cell lines and xenografts of the childhood cancer neuroblastoma (NB). Further, by using the secretome as a discriminator for beneficial versus adverse effects of senescence, drugs with a favorable SASP shall be identified.

Methods and Results: We here demonstrate that metronomic application of broadly used chemotherapeutic drugs induces therapy-induced senescence specifically in MYCN-amplified, but not in MYCN non-amplified NB cell lines. Senescence is characterized by high activity of the senescence-associated-beta-galactosidase, cell cycle arrest, p21 up-regulation and induction of DNA double-strand breaks. Secretome analysis identified low-dose topotecan (TPT) as an inducer of a favorable SASP due to a lack of NFkB1/p50 activation. In contrast, BrdU treatment leads to NFkB1/p50 activation and secretion of unfavorable, tumor-promoting factors. In addition, TPT-treated senescent tumor cells act growth-inhibitory in a dose-dependent manner on non-senescent tumor cells. MYCN oncogene amplification, a hallmark of high-risk neuroblastoma, and MYCN expression are significantly reduced, supporting a transition to a more favorable phenotype. Further, metronomic TPT treatment leads to senescence selectively in tumor cells, complete remission and prolonged survival in a xenotransplant-model for aggressive neuroblastoma.

Conclusions: This new senescence-promoting mode-of-action of metronomic drug treatment is clinically relevant as metronomic regimens are increasingly implemented in therapy protocols of various cancer entities and are considered as feasible additional treatment option with little side effects.

No conflict of interest.

1402

ORAL

Design of the Myechild trial, an international randomised phase III clinical trial in children with acute myeloid leukaemia incorporating an embedded dose finding study

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Background: Acute myeloid leukaemia is a rare disease in children but is a significant cause of childhood cancer mortality. Whilst advances in treatment have led to an improvement in overall survival (OS), the cumulative incidence of relapse (CIR) remains unacceptably high with relapsed disease the commonest cause of death.

Methods: This trial is designed to test strategies in both induction and consolidation for their value in improving survival without significantly increasing toxicity by evaluating treatments in four randomised comparisons.

The embedded dose finding study aims to identify the optimum number of doses of Gemtuzumab ozogamicin (GO) that can be safely combined with induction chemotherapy, which then forms part of the induction randomised comparisons. A rolling design is applied to the dose finding study to reduce the need to pause recruitment between cohorts. In order to determine patient's treatment allocation they will be risk stratified according to their cytogenetic, molecular characteristics and morphological response.

Results: 700 patients will be randomised to the trial over 6 years. Randomisation 1 will use a probability based approach to assess event free survival (EFS). It is estimated that 280 events will be observed, if the observed hazard ratio (HR) was 0.89 or better in favour of a particular treatment we could be >80% sure that this is the more effective treatment. It is anticipated that around 550 patients will enter randomisation 2. Given the higher dose of GO leads to an increase in EFS from 60% to 70% then this number of patients will provide >84% power to detect this difference on a 2-sided α of 0.15. Around 60% of patients will be eligible for consolidation randomisation 3, with 140 events expected based on a historical relapse rate of 33%. A probability based approach will be applied to this randomisation. An observed HR of 0.86 or less would be required to be 81% sure that the treatment was better. If the true HR was 0.8 in favour of a particular treatment then we have a 66% chance of achieving this level of certainty. We expect 150 high risk patients to be eligible for the stem cell transplant conditioning randomisation. This randomisation will assess both toxicity and efficacy. With an estimated toxicity rate in the control arm of 40%, if the true toxicity rate in the control arm is 20% then there would be 85% power to detect this difference with a 2-sided α of 0.15. The trial will analyse each randomisation in its own right and where appropriate stratified by the treatment that each patient has received in former randomisations. This approach is considered appropriate as there is no reason to anticipate any interaction between treatments in different randomisations.

Conclusion: This design will allow multiple randomised comparisons to be evaluated effectively and treatment pathways to be established.

No conflict of interest.

1403

ORAL

Pharmacokinetics and pharmacodynamics study of lipegfilgrastim (XM22) in children with Ewing family of tumors or rhabdomyosarcoma

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Background: Neutropenia is a common toxicity of chemotherapy and limits optimal dosing. Lipegfilgrastim (XM22) is a long-acting granulocyte colony-stimulating factor developed for prevention and management of chemotherapy-induced neutropenia. This completed phase 1, multinational, open-label, single-arm study (NCT01585649) examined the pharmacokinetics (PK), safety, efficacy, and pharmacodynamics (PD) of a single subcutaneous lipegfilgrastim injection in pediatric patients.

Materials and Methods: Patients age 2 to 17 y with Ewing family of tumors or rhabdomyosarcoma scheduled to receive myelosuppressive chemotherapy were given a single subcutaneous injection of lipegfilgrastim (100 μ g/kg) 24 h after the last chemotherapy treatment in wk 1. Patients were stratified into 3 age groups: 2 to <6, 6 to <12, and 12 to <18 y. Primary endpoint was PK; other endpoints were PD (absolute neutrophil count [ANC]), safety, and efficacy (incidence of febrile neutropenia [FN], neutropenia).

Results: 21 patients were enrolled and received lipegfilgrastim, 7 in each age group. PK results were comparable across age groups (Table). Most investigator-reported adverse events were related to chemotherapy and not to lipegfilgrastim. The only serious adverse events were neutropenia and FN (3/21 patients). Per central laboratory findings ($n=20$), FN, very severe neutropenia (ANC $<0.1 \times 10^9/L$), and severe neutropenia (ANC $<0.5 \times 10^9/L$) occurred in 4 (20%), 4 (20%), and 14 (70%) patients, respectively. Stratification by type of chemotherapy showed that VIDE treatment (predominantly used in children 6–18 y) was associated with the highest FN incidence (4/12), particularly in patients 12 to <18 y (3/6). Changes in ANC varied by type of chemotherapy (Table).

Conclusions: Our results support the use of a 100 μ g/kg dose of lipegfilgrastim in children. A single injection of lipegfilgrastim was generally safe and well tolerated in this population. The PD effect of lipegfilgrastim seems to depend on the type of chemotherapy and less on age. The incidence of FN was aligned with published data, in which pediatric

Table (abstract 1403).

	Age group (y)			Type of chemotherapy		
	2 to <6 (n = 7)	6 to <12 (n = 7)	12 to <18 (n = 7)	I/A (n = 5)	V/A (n = 4)	VIDE (n = 12)
Pharmacokinetics						
Mean T_{max} , h (SD)	50.3 (49.5)	45.4 (27.2)	82.2 (42.1)			
Geometric mean C_{max} , ng/mL (95% CI)	243 (128–460)	256 (128–510)	225 (90–560)			
Geometric mean AUC_{0-inf} , ng*h/mL (95% CI)	26,050 (4,535–149,621)	29,985 (14,841–60,584)	38,365 (20,445–71,992)			
Pharmacodynamics						
Mean ANC nadir, $\times 10^9/L$ (SD)	0.88 (0.76)	0.21 (0.35)	0.37 (0.77)	1.23 (0.71)	0.85 (0.93)	0.09 (0.08)
Mean duration of severe neutropenia, days (SD)	0.7 (1.2)	2.4 (1.9)	3.1 (1.9)	0 (0.0)	0.5 (0.6)	3.4 (1.4)

Chemotherapy abbreviations: A, actinomycin; C, cyclophosphamide; D, doxorubicin; E, etoposide; I, ifosfamide; V, vincristine.

patients with Ewing sarcoma developed FN after 78% of VIDE cycles with pegfilgrastim administration and 56% of cycles with filgrastim.

Conflict of interest: Sponsor: Merckle GmbH, Teva ratiopharm. Corporate-sponsored Research: Margarita B. Belogurova and Zoryana P. Kizyma have received grants from Teva. Other Substantive Relationships: Anton Buchner, Peter Bias, and Andreas Lammerich are employees of Teva ratiopharm.

1404

ORAL

Calibrated integrated backscatter as a marker of myocardial fibrosis and left ventricular diastolic function in adult survivors of childhood leukaemias

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Background: Alteration in myocardial extracellular matrix due to fibrosis may alter ventricular stiffness and compliance in childhood cancer patients receiving anthracycline therapy. This study tested the hypotheses that calibrated integrated backscatter (cIB) as a marker of myocardial fibrosis is altered in adult survivors of childhood leukaemias and related to diastolic ventricular mechanics.

Material and Methods: Ninety-four (53 males) adult survivors of childhood leukaemias aged 22.4 ± 5.5 years with normal left ventricular (LV) ejection fraction and 66 (36 males) healthy controls were studied. Calibrated integrated backscatter intensity was measured as an index of myocardial fibrosis. Left and right ventricular (RV) diastolic mechanics in terms of early and late diastolic strain rates were interrogated using speckle tracking echocardiography.

Results: Compared with controls, patients had significantly greater myocardial cIB of the ventricular septum (-26.3 ± 2.9 dB vs -28.5 ± 2.5 dB, $p < 0.001$), LV posterior wall (-24.4 ± 2.7 dB vs -27.2 ± 1.8 dB, $p < 0.001$) and average cIB of the two sites (-25.4 ± 2.7 dB vs -27.8 ± 2.0 dB, $p < 0.001$). Patients had significantly lower LV longitudinal ($p = 0.001$), radial ($p < 0.001$), and circumferential ($p = 0.002$) early diastolic strain rates, circumferential late diastolic strain rate ($p = 0.002$), peak systolic twisting ($p = 0.004$) and diastolic untwisting velocities ($p = 0.004$), and RV free wall longitudinal early diastolic strain rate ($p = 0.048$) than controls. For the entire cohort, the average myocardial cIB correlated inversely with LV radial early diastolic strain rate ($r = -0.18$, $p = 0.021$), peak systolic twisting velocity ($r = -0.21$, $p = 0.007$) and peak diastolic untwisting velocity ($r = -0.28$, $p < 0.001$), and not RV diastolic deformation indices ($p > 0.05$).

Conclusion: Increased cIB suggestive of myocardial fibrosis occurs in adult survivors of childhood leukaemias and is related to impaired LV diastolic mechanics.

No conflict of interest.

1405

ORAL

Burnout of parents having children with cancer

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Background: Cancer diagnosis in child and stressors associated with treatment process have a significant impact on psychosocial functioning

of parents. Aim of the study was to investigate the level of parents' burnout and relationships between family demographics data and child's illness variables.

Material and Methods: The Shirom-Melamed Burnout Measures (SMBM), and structured questionnaire on demographical and child's illness data were completed by 101 parents (56.4% mothers) of 75 children with cancer (mean of age=10.2 yrs; 65.3% boys). Children were treated in single pediatric onco/hematology centre. Mean time from diagnosis was 20.3 month. Statistical analyses (Pearson's r, t-test, analysis of variance, test NIR) were performed using SPSS 17.

Results: General burnout level of parents was high ($M = 2.89$). Mothers' general burnout level was significantly higher than fathers ($p < 0.05$). In such burnout subscales as physical fatigue and cognitive weariness comparable high level was observed in both parents (79.3% mothers and 62.8% fathers). 46.5% of fathers revealed higher level in emotional exhaustion scale than mothers. No significant differences were found between mothers' and fathers' burnout subscales levels. As a risk factors of high level of mothers' burnout: young age of sick child, lonely parenting, financial difficulties, frequent hospitalisations and anxious children's behaviour were indicated. In fathers', higher level of general and emotional burnout was related to occasional staying with child in hospital, and lack of adequate information during course of disease. Mothers reported higher number of emotional support resources than fathers.

Conclusions: 1. High level of burnout among mothers and fathers of children with cancer concerned near 70% of parents. 2. Mothers assist their children in hospital more frequently than fathers, and had more occasion for receiving different emotional support. 3. Parents should be monitored on burnout level and offered adequate support. 4. Especially fathers, in the often mother-dominated pediatric setting should receive more attention in establishing psychosocial support.

No conflict of interest.

Poster Session (Monday, 28 September)

Paediatric Oncology

1406

POSTER

Childhood Orbital Rhabdomyosarcoma. Report from Children's Cancer Hospital-57357-Egypt

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Background: Rhabdomyosarcoma (RMS) in the head and neck especially orbit represents a major anatomic site for this tumor in pediatrics. Orbital RMS is the most common primary orbital malignancy in children with approximately 35 new cases per year.

Objectives: The aim of this work is to study cases of orbital RMS and assess epidemiology, clinical and pathological characteristics as well as survival outcomes.

Methods: Patients diagnosed with orbital RMS between July 2007 and July 2012 follow-up till July 2014. They were treated according to IRS-IV and IRS V protocols. Case report forms were analyzed and treatment outcome, OS and FFS for patients were analyzed.

Results: Seventeen orbital RMS patients were diagnosed at the mentioned period. Complete remission was identified in 7 (41.2%) cases, Partial remission in 4 (23.5%) cases and progressive disease in 4 (23.5%) cases