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research abstracts and case presentations

SIOPEN ANNUAL GENERAL MEETING LJUBLJANA
4 - 6 October, 2023

EUSA Pharma · RECORDATI RARE DISEASES GROUP · JUNAKI 3. NADSTROPJA · SIOPEN R-NET · SIOP Europe the European Society for Paediatric Oncology

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research abstracts

Poster presentation

The prognostic value of detecting isolated neuroblastoma cells in bone marrow by immunocytochemistry

Clinical Research

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ABSTRACT

Background

In neuroblastoma, 40% of patients have metastatic disease at diagnosis, 70% of whom have bone marrow (BM) involvement.

BM evaluation (BME) is crucial for correct staging, definition of a risk-adapted treatment strategy, and follow up. The gold standard of BME is cytology/morphology (CM), which consists of cytological and morphological examination of BM aspirates and immunohistochemistry (IHC) of BM trephines. Other techniques include BM immunocytochemistry (ICC), flow cytometry, and automatic immunofluorescence plus FISH.

In this study, we sought to evaluate the sensitivity, specificity and prognostic impact of ICC BME as compared to the standard techniques.

Methods

We studied all patients with peripheral neuroblastic tumors diagnosed and treated at Institut Curie between 2000 and 2020, with available data on BME. BM was studied by CM for initial staging according to INRG criteria and ICC by antiGD2 antibody.

Results

Among 390 patients (214 boys/176 girls; mean age 40 months, range 0-330 months; INRG stage L1 55,L2 114,M 178,Ms 32, localised disease 11; median FU 100 months, range 2–250 months), 1095 BM samples were analysed by cytology/morphology+IHC (CM+ in case of positivity of any of these analyses) and/or by ICC (ICC+ according to previously published criteria).

At diagnosis, 134 were CM+ICC+, 213 CM-ICC-, 17 CM+ICC-, and 26 CM-ICC+ (x2-test, $p<0.0001$). Among the 26 CM-ICC+ patients, 12 had metastatic and 14 had localised disease according to clinical/radiological criteria.

During treatment/follow-up, after induction or first line chemotherapy, 23 remained CM+ICC+, 337 were CM-ICC-, 12 CM+ICC-, and 18 CM-ICC+ (none of whom were CM-ICC- at diagnosis).

In this cohort, 5-year overall survival (OS) of patients with CM-ICC+ was not statistically different from CM-ICC- (CM+ICC+: 47± 4.6%; CM-ICC-: 71±2.4%; CM+ICC-: 44% ±12%, CM-ICC+: 78± 8.5%; CM-ICC+ vs. CM-ICC-, P=0.3).

Among the 180 patients with clinically localised disease, isolated ICC positivity was not associated with a statistically significant worse 5-year OS (92% versus 100%).

Conclusion

The isolated presence of NB cells in BM detected by ICC (anti-GD2) is not associated with a poorer prognosis in this study. Further biological analyses, including single-cell RNAseq, will determine the role of disseminating tumor cells in BM.

Poster presentation

Atypical neuroblastoma: screening of urinary catecholamine excretion and mIBG avidity at diagnosis: a retrospective study

Clinical research

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ABSTRACT

Background

In neuroblastoma (NB), urinary catecholamine excretion and mIBG avidity, proportional to norepinephrine transporter's (NET) expression, have been used for decades as diagnostic tools. Recently, cellular plasticity has been described, with a mesenchymal phenotype related to an absence of enzymes involved in catecholamine synthesis and an absence of NET. The frequency and prognostic impact of atypical NB, without catecholamine excretion and/or without mIBG avidity, remains to be determined.

Aims

1. To determine the frequency and prognosis of atypical NB.
2. To investigate the urinary catecholamine profile and to evaluate its correlation with mIBG avidity.

Methods

From 2000 to 2020, 253 children treated for NB at Institute Curie, France, were analyzed for catecholamine excretion and mIBG avidity.

Results

62 of 253 NB had atypical features: 16 without mIBG avidity with positive catecholamine excretion, 35 without catecholamine excretion with mIBG avidity, and 11 with neither mIBG avidity nor catecholamine excretion. Concerning atypical NB, 63% had INRG stage L1/2 (n=37), 27% had stage M (n=16), 10% had stage MS (n=6), versus typical NB (n=191) which 28% had stage L1/2 (n=52), 61% had stage M (n=114) and 11% had stage MS (n=21). NMYC amplification, segmental and numeric genomic profile were found in 12%, 48% and 52% of patients with atypical NB, versus 31%, 74% and 26% of patients with typical NB, respectively. OS and EFS were better in atypical than typical NB with 5-year OS of 87% vs 64% ($p<0.0007$) and EFS of 77% vs 51% ($p<0.0009$). Catecholamine excretion in overall NB was dominated by elevated vanillylmandelic acid/homovanillic acid (VMA/HVA) in 53% (n=103), dopamine in 41% (n=80), with only 2% epinephrine and 4% norepinephrine excretion predominance respectively. mIBG non-avid tumors had catecholamine excretion in 59% (n=16), with elevation of VMA/HVA in 69% (n=9). Elevated dopamine excretion had worse 5-year OS comparatively to VMA/HVA positivity, 43% and 80% respectively ($p<0.0001$).

Conclusion

Atypical NB are observed in 25% of patients, have more favorable tumor features and are associated with a better prognosis. Catecholamine excretion profiles reveal clinical and biological subgroups which might be of clinical relevance. Complementary biological studies including single cell RNAseq analysis will provide insight into disease-associated features for prognostic and therapeutic value.

Poster presentation

Anaplastic lymphoma kinase (ALK) inhibitors in patients with neuroblastoma: initial experience of the Hellenic Society of Pediatric Hematology - Oncology (HESPHO)

Clinical research

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ABSTRACT

Background and Aims

Genetic changes (mutations/amplification) in the ALK—oncogene occur in 10-15% of newly diagnosed patients with HR-neuroblastoma and in > 25% of relapses. Following initial promising results, administration of ALK-inhibitors started in Greece for selected neuroblastoma patients, following individual patient approval by the National Medicines Agency. This study aims to present the initial national experience.

Methods

We retrospectively recorded epidemiological/clinical characteristics and disease outcome of patients with neuroblastoma that received ALK-inhibitors in Greek Pediatric Hematology-Oncology Departments (7).

Results

We registered six patients (4 boys, 5 initially high risk) with median age at diagnosis 4.15 years (1.9-10.1). Primary sites were adrenal gland (4) and posterior mediastinum (2). Metastatic disease was present at diagnosis in 5/6 (bones:1, bone marrow:3, bones-bone marrow-skin:1). One patient, initially L2 MYCN-NA, developed metastatic relapses (>5) and received three ALK inhibitors. Prognostic molecular markers detected were Myc-N amplification (2), 1p-deletion (2), 2p-gain (1) and 17q-gain (1). 5/6 received first line treatment as per SIOPEN-HR protocols. 3/6 achieved first complete remission. All received ALK-inhibitors as a more than third-line treatment, based on ALK expression in immunohistochemistry (3), NGS (2) or without confirmation (1).

Crizotinib (2), Ceritinib (1) and Lorlatinib (6) were given, either as monotherapy or with chemotherapy (topotecan-cyclophosphamide: 2, ifosfamide,-carboplatin-etoposide: 1). One patient received all three inhibitors and one patient two (Crizotinib, Lorlatinib). Serious side effects were hypotension and hypoxemia, the last being the cause for treatment discontinuation in one patient.

Two patients achieved complete remission with monotherapy (Lorlatinib:1 and Crizotinib:1) for 39 and 27 months respectively. Two patients achieved partial remission (Lorlatinib), for 38 months of monotherapy and 2.9 months with Cyclo/Topo respectively. All four had started with disseminated disease. Three patients died of disease progression. 2/3 patients with long remissions (39 and 38 months on Lorlatinib) were ALK-amplified confirmed by NGS.

Conclusions

Although our results come from a small series of heterogeneous patients, they indicate that ALK-inhibitors can improve prognosis and prolong survival of selected patients with high-risk neuroblastoma. Complete ALK molecular analysis (rather than immunohistochemical detection alone) is necessary for patient selection and improved outcome. International studies are ongoing.

Oral presentation

Combining CD47 blockade with chemoimmunotherapy in preclinical neuroblastoma models

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Basic research

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ABSTRACT

Background and aims
Although survival rates for high-risk neuroblastoma (NB) patients have improved, a subset remains with chemotherapy resistant disease whose prognosis remains poor. Dinutuximab-beta is an immunotherapy that binds to GD2, a highly expressed antigen on most NB tumours. Combining dinituximab-beta with chemotherapy, such as temozolomide and irinotecan, improves progression-free survival and has become an established treatment backbone at first relapse. Anti-GD2 activates macrophages, an immune cell, causing tumour cell death by antibody-dependent cellular phagocytosis. CD47 is a "Don't Eat Me" signal overexpressed by NB cells to supress killing by macrophages. We aim to evaluate addition of CD47 targeted agents to chemoimmunotherapy in models representative of the NB immune environment.

Method

Genetically engineered mouse models (GEMM) were used to generate 3 NB cell lines; TAM6 and WIN6, 2 chemoresistant Th-MycN$^{+/-}$/Th-AlkF$^{1147L/-}$ neurospheres in 129SvJ/X1 and C57Bl6 respectively, and 9464D-GD2, derived from tumours from Th-MycN$^{+/-}$ C57Bl6 mice and transduced to overexpress GD2. Targeting of CD47 was performed *in vitro* with the MIAP301 antibody and *in vivo* using a mouse specific SIRPa-Fc fusion protein. The mouse homolog of dinituximab-beta, 14G2a was used for *in vitro* and *in vivo* studies. In flow-based *in vitro* phagocytosis assays, NB cells are co-cultured with murine macrophages and treated with anti-GD2 and/or anti-CD47. The efficacy of combining temozolomide, irinotecan, anti-GD2 and anti-CD47 was assessed *in vivo*.

Results

All 3 cell lines were positive for GD2 and CD47 *in vitro* and *in vivo.* Interestingly, 9464D-GD2, which is most resistant to chemoimmunotherapy *in vivo,* was resistant to phagocytosis *in vitro* with anti-GD2 and/or anti-CD47. Moreover, both TAM6 and WIN6 show additive phagocytosis with combination antibodies. Partially effective regimes of chemoimmunotherapy backbones have been established for *in vivo* neurospheres, allowing evaluation of CD47 inhibition in complex multi-arm animal studies. Using multiparameter flow cytometry and unbiassed cluster analysis, *in vivo* models show paucity of infiltrating lymphocytes but significant populations of tumour resident myeloid populations.

Conclusion

We have established models of immune competent and immune cold tumours representative of human NB. Preliminary studies indicate initial proof of concept of addition of CD47 targeting reagents to backbone GD2 targeting chemoimmunotherapy in the relapse setting.

Oral presentation

Urinary catecholamine metabolites as marker for relapse in high-risk neuroblastoma

Clinical research

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ABSTRACT

Background

Urinary catecholamine metabolites are useful diagnostic and prognostic biomarkers for neuroblastoma. Currently, catecholamines are not included in response criteria for therapy. It is unclear whether urinary catecholamines are useful markers for detecting neuroblastoma relapse.

Methods

Urinary catecholamine status was determined at diagnosis, end of induction, complete remission (CR) and relapse in 153 high-risk neuroblastoma patients that were treated according to the NBL2009 protocol. The catecholamine metabolites homovanillic acid, vanillylmandelic acid, dopamine, 3-methoxytyramine, norepinephrine, epinephrine, normetanephrine and metanephrine were measured. Catecholamine status was defined as positive if at least one metabolite was above the reference value. CR was defined as SIOPEN score £ 1 on MIBG scan in combination with a negative bone marrow biopsy.

Results

At diagnosis, 150 of 153 patients had a positive catecholamine status (98%), compared with 77 of 97 at end of induction (79%), 54 of 86 at CR (63%), and 29 of 48 at relapse (60%). Catecholamine status at diagnosis and at end of induction was not associated with relapse-free survival or overall survival (OS) in the overall high-risk cohort. However, in patients with MYCN-amplified tumors, positive catecholamine status at end of induction was associated with reduced relapse-free survival (median survival 26.3 months versus 31.2, 58.7, and 46.6 months for patients with MYCN-amplified tumors with negative catecholamine status and with MYCN-non amplified patients, P=0.04). At CR, patients with positive catecholamine status had a median relapse-free survival of 23.8 months versus 36.3 months for patients with negative catecholamine status, regardless of MYCN status. Moreover, positive catecholamine status was associated with lower relapse-free survival (hazard ratio for relapse 3.4, P<0.05) and lower OS (hazard ratio for death 3.5, P=0.02).

Conclusions

Positive urinary catecholamine status at time of CR predicted poor relapse-free survival and OS. Remarkably, the percentage of catecholamine negative urine was higher at relapse than at initial diagnosis, suggesting differences in tumor biology.

Poster presentation

Plasma-derived exosome proteins with diagnostic and prognostic value for neuroblastoma patients

Clinical research

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ABSTRACT

Background and Aims

Neuroblastoma (NB) is the most common extra-cranial solid tumor during infancy, causing up to 10% of mortality in children. NB shows notable heterogeneity with regard to histology and clinical behavior, ranging from low risk (LR) localized tumors to high risk (HR) disease, characterized by aggressive metastatic phenotype, resistance to treatment and fatal relapse occurrence. Risk stratification demands the highest accuracy, as it will determine the therapeutic treatment. Circulating NB-derived exosomes carry proteins (Exo-prot) reflecting the status of the tumor cell of origin, thus representing a source of biomarkers. The purpose of this study is to characterize for the first time the Exo-prot specifically expressed in NB patients associated with tumor phenotype and disease stage.

Methods

We isolated exosomes from plasma specimens of 24 HR-NB and 24 LR-NB patients at the onset, and 24 age-matched healthy controls (CTRL). Exo-protein expression was measured by liquid chromatography-mass spectrometry. We used two different missing values imputation methods for the statistical analysis.

Results

Our results identified 458 exo-prot detectable in at least one NB patient or CTRL subject. Differential expression analysis showed that NB patients are characterized by altered expression of exo-prot involved in inflammatory processes, cell proliferation and apoptosis and extracellular matrix interactions. Among them, ROC analysis showed that NCAM (AUC 0.83), NCL (AUC 0.85), VASP (AUC 0.8) and DCN (AUC 0.75) are strong diagnostic markers discriminating NB patients and CTRL subjects.

By comparing HR- and LR-NB patients, we observed differentially expressed exo-prot acting in immune response, cell migration and cytoskeletal organization. Among them, ROC analysis showed that MYH9

(AUC 0.95), FN1 (AUC 0.89), CALR (AUC 0.94), LTBP1 (AUC 0.78) and AKAP12 (AUC 0.74) have a significant prognostic value.

Conclusions

We characterized the protein cargo of patient-derived exosomes. We demonstrated that NB-derived exosomes show altered expression of exo-prot involved in pro-tumoral processes and, among them, we identified 4 diagnostic NB markers. We also demonstrated that exosomes of HR-NB patients have an aberrant expression of proteins contributing to cell invasion and metastasis. Among them, we identified 5 exo-prot that discriminate HR- and LR-NB patients with high sensitivity and specificity.

Poster presentation

LC-MS/MS detection of circulating GD2 ganglioside in plasma samples from neuroblastoma patients in age-matched healthy children - diagnostic and prognostic evaluation

Clinical research

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ABSTRACT

Background and Aims

GD2 is shed into circulation from neuroblastoma (NB) cells and the C18 and C20 GD2 lipoforms can be simultaneously measured by a validated LC-MS/MS method. This study aims at evaluating the diagnostic/prognostic power of circulating GD2 levels in children with NB, treated according to SIOPEN trial.

Methods

Fifty uL of PB and BM-derived plasma of 83 children with NB (15 L1, 15 L2, 48 M and 5 MS with a median age of 37.3 months) and PB-derived plasma of 83 age-matched healthy children were analyzed by LC- MS/MS. Thirty samples of the 48 stage M patients were also collected at post-induction therapy (PIT).

Results

C18 and C20 GD2 concentrations were significantly higher in children with NB than in age-matched controls (P<0.0001). C18 and C20 median concentrations in NB samples were 244.9 and 1.5 nM, respectively. C18 and C20 values significantly correlated to each other, particularly in NB patients (Spearman r=0.93 *vs.* r=0.7 in controls) and C18/C20 ratio was similar in both NB and controls (range 37.4-502.3 *vs* 36.4-473). C18 and

C20 values were no significantly different in male and female or in infants and children. Importantly, circulating C18 (r=0.95) and C20 (r=0.83) lipoforms strongly correlated between PB and BM. At NB onset, GD2 concentration was significantly higher in stage M patients, *MYCN* amplified cases (*P<0.001*) and deceased patients (*P=0.0038*).

For the diagnostic potential, ROC analysis showed a cut-point of 44.1 (C18) and 0.4 nM (C20), able to discriminate with high specificity and sensitivity NB from controls. Conversely, for the prognostic potential ROC analysis failed to find prognostic cut-points, independently from stage or *MYCN* amplification. C18 and C20 concentrations at PIT were strongly reduced in stage M patients, but the absolute values or the delta between onset and PIT levels were unable to predict survival.

Conclusion

Measurement of circulating GD2 by LC-MS/MS lacks independent prognostic power, but it is a cost-effective powerful diagnostic tool, which can be performed by micro sampling and, thus, easily applied to clinical settings. As GD2 levels strongly correlated between BM and PB, GD2 analysis can be performed in PB samples, ensuring a non-invasive diagnostic evaluation.

Poster presentation

BEST ORAL PRESENTATION AWARD AMG 2023

Real-world data on chemo-immunotherapy for patients with relapsed high-risk neuroblastoma included in the SACHA - France study

Clinical research

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ABSTRACT

Background and aims

The addition of dinutuximab beta (DB) to temozolomide-based chemotherapy showed increased anti-tumor activity and progression-free survival in patients with relapsed/refractory high-risk neuroblastoma in the SIOPEN BEACON- Immuno trial. Since trial recruitment stopped in February 2021, no access to chemo- immunotherapy was available in Europe within clinical trials. To address

this issue, in October 2021 the Neuroblastoma Committee of the French Society of Pediatric Oncology (SFCE) and EUSA Pharma established a nationwide compassionate use program (based on individual patient approval) to allow access to DB + Topotecan/Cyclophosphamide (TC) to patients after first-line relapse therapy (as in the BEACON-Immuno roll-over arm). Since December 2022, based on BEACON-Immuno trial results, prescription of DB + temozolomide-based chemotherapy (TOTEM or TEMIRI) at first relapse was also allowed.

Methods

We here report our nationwide compassionate use program. Real-world anti- tumor activity and toxicity of DB combined with chemotherapy was collected within the SACHA-France study (NCT04477681). The SACHA-France study is a prospective, multicenter, national observational registry that collects clinical safety and efficacy data on innovative anticancer therapies first approved in adults after 2007 that are administered to patients ≤ 25 years-old with pediatric malignancies (solid tumor or leukemia) and prescribed either as compassionate or off-label use. This registry is open in all 30 SFCE centers.

Results: Forty-four patients with high-risk neuroblastoma from 18 SFCE centers have received DB + chemotherapy at the time of relapse, combined with TC (n=28) or TOTEM/TEMIRI (n=16) (datalock: 23rd July 2023). Noteworthy, 27 patients started their chemo-immunotherapy after January 2023 and data on response and survival are currently being collected and analyzed. Global updated results on activity and toxicity of DB + chemotherapy is currently ongoing and will be presented at the SIOPEN AGM.

Conclusions

This is the first nation-wide compassionate use program on DB + chemotherapy in patients with relapsed high-risk neuroblastoma. Moreover, it includes a unique cohort of patients treated with DB + TC. This program is a proof of concept that underlines the crucial importance of the collaboration between academia and pharmaceutical companies to fill the gap between clinical trial end of enrolment and drug approval in patients with unmet clinical needs.

Poster presentation

Overcoming analytical challenges for the measurement of urinary catecholamine metabolites HVA and VMA by liquid chromatography-tandem mass spectrometry: a tool for the diagnosis of neuroblastic tumors

Clinical research

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ABSTRACT

Background and aims

Urinary catecholamine metabolites are well-established biomarkers for neuroblastoma (NB). Patterns of expression of these metabolites can provide diagnostic as well as prognostic value. SIOPEN catecholamine working group is promoting harmonization between reference laboratories for the biochemical diagnosis setting liquid chromatography-tandem mass spectrometry (LC-MS/MS) as the gold standard method. Nevertheless, the majority of laboratories still use high-performance liquid chromatography (HPLC) which is more unspecific and round robin tests between reference laboratories highlighted HPLC and LC-MS/MS cannot be considered interchangeable. The analysis of homovanillic and vanillylmandelic acid (HVA and VMA) by LC-MS/MS might be particularly challenging because of their negative ionization characteristics. We have developed a novel method to overcome these technical issues and facilitate harmonization between laboratories.

Methods

A LC-MS/MS method for the quantitative determination of HVA and VMA from 40 µL urine has been developed using a rapid sample preparation including a simple derivatization step at room temperature followed by analysis on a Thermo Fisher Quantiva LC-MS/MS system. Detection of analytes and their deuterated internal standards was made by using multiple reaction monitoring (MRM) using positive ionization. The method was validated according to EMA guidelines and has been applied to 120 clinical samples (of which 60 from patients with NB at diagnosis) and EQA samples. Additionally, it has been tested in a round-robin evaluation with 36 samples, involving reference laboratories. The results obtained on clinical samples obtained by LC-MS/MS were correlated with those obtained by HPLC-EC by Passing-Bablok linear regression.

Results

The LC-MS/MS method results robust and was validated in a large calibration range (4.61-830 and 4.44-800 µmol/L, respectively) using QCs and EQA samples from UKNEQAS. A linear relationship between LC-MS/MS and HPLC-EC was obtained for both HVA (r=0.944, P<0.0001, 95% CI 0.5361-0.6178 VMA) and VMA (r=0.941, P<0.0001, 95% CI 0.5831-0.7182) but results obtained by LC-MS/MS displayed a higher diagnostic accuracy for NB and can be considered as interchangeable with those of reference centers using LC-MS/MS.

Conclusions: The novel LC-MS/MS method is a useful tool for an accurate measurement of HVA and VMA and could help in harmonization between laboratories involved in the biochemical diagnosis of NB.

Poster presentation

Locoregional failure in high-risk abdominal neuroblastoma using highly conformal image-guided radiotherapy – outcome after centralization of care in the Netherlands

Clinical research

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ABSTRACT

Background and aims

Advanced radiotherapy modalities to irradiate neuroblastoma have stepwise replaced 2D-conventional and 3D-conformal techniques. The aim of this study was to investigate the locoregional failure (LRF) rate and pattern of failure after highly-conformal image-guided radiotherapy, applied since centralization of neuroblastoma care in the Netherlands in 2014.

Methods

All patients with high-risk abdominal neuroblastoma treated with curative intent between January 2015 and March 2022 were eligible. Edited gross tumor volumes were defined by pre-operative imaging, endorsed by input from surgeons and radiologists, and adjusted for post-operative anatomical shifts. For clinical, internal, and planning target volume (CTV, ITV, and PTV), 0.5 cm, 4DCT-based, and 0.3–0.5 cm margins were added, respectively. Prescription dose was 21.6/1.8 Gy after complete macroscopic excision (CME), followed by 14.4/1.8 Gy in case of residual tumor ≥1 cm^3 (IME; incomplete macroscopic excision). Intensity-modulated arc therapy combined with daily 3D online position verification/correction was applied. Three-year locoregional failure rate, event-free survival (EFS), and overall survival (OS) were calculated.

Results

A total of 81 patients were included (median age at radiotherapy: 4.1 years, IQR 2.7–5.9), 46 (57%) with CME and 35 (43%) with IME (median residual volume 10.1 cm^3, IQR 4.5–34.5). Mean follow-up was of 5.9 years. Three-year LRF rate was 9.9% (95% CI 3.4-16.5%) and did not differ significantly between CME (8.8%, 95% CI 0.5–17.2%) and IME (11.4%, 95% CI 0.7–22.1%) groups, P=0.71. For the total group, three-year EFS was 52.9% (95% CI 64.1–41.6) and three-year OS was 67.8% (95% CI 58.1–79.1%). Eight patients presented with a LRF (three isolated locoregional and five combined with distal failure), all of which occurred within two years from diagnosis.

Conclusions

In a setting of nationally centralized neuroblastoma care, highly-conformal target volumes, using CTV margins of 0.5 cm, combined with image-guided radiotherapy, results in excellent locoregional control rates compared to current literature. A 14.4 Gy boost dose to any residual tumor ≥1 cm^3 may compensate for a higher risk of locoregional failure.

Oral presentation

Bone marrow infiltration by sensitive RT-qPCR correlates with poor outcome in neuroblastoma with post-induction SIOPEN score ≤3

Clinical research

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ABSTRACT

Background and aims

Reverse transcriptase-quantitative PCR (RT-qPCR) is a sensitive method for detecting sub-microscopic bone marrow (BM) infiltration in neuroblastoma (NBL). The aim was to investigate the added diagnostic yield and prognostic value of RT-qPCR compared to conventional methods in patients with high-risk NBL.

Methods

Patients with high-risk NBL who were enrolled in the prospective Minimal Residual Disease study (2008–2022) at diagnosis and/or post-induction, were included. BM samples from both iliac crests were analysed by immunohistochemistry plus cytomorphology (IHC+CM) and RT-qPCR (mRNA panel: *PHOX2B*, *Tyrosine Hydroxylase*, *CHRNA2,* and *GAP43*). SIOPEN scores were collected from paired (≤15 days interval) meta-[^{123}I]Iodobenzylguanidine (MIBG) scans. After excluding paired examinations with missing (IHC+CM, RT-qPCR, and/or MIBG) results, diagnostic yield of each method was analysed at diagnosis and post-induction. After single imputation of missing results in the post-induction cohort, five-year recurrence-free survival (5y-RFS) was calculated, for patients with the following conditions: SIOPEN score ≤3 vs. >3 and RT-qPCR positive vs. negative.

Results

Of the 164 patients in the total cohort (95% stage 4), 157 were included at diagnosis and 134 at post-induction. At diagnosis and post-induction, 137 and 67 patients had complete results with additional cases of BM involvement being detected by RT-qPCR-only in 10 (7%) and 8 (12%), respectively. In total, there were nine cases with BM involvement by MIBG-only, all concerning MIBG uptake outside the iliac crests. In patients with a post-induction SIOPEN score ≤3 (n=92), a positive RT-qPCR result was associated with a significantly reduced 5y-RFS compared to a negative result: 28% vs. 60%, respectively, P<0.01. A similar association was seen in patients with a SIOPEN score >3 (n=42, 5y-RFS 14% for a positive RT-qPCR vs. 43% for a negative RT-qPCR), however not statistically significant in this small cohort.

Conclusions

RT-qPCR detects additional cases of BM-involvement in high-risk NBL, both at diagnosis and post-induction. Addition of RT-qPCR showed significant prognostic value in patients with a post-induction SIOPEN score ≤3, which may improve risk classification within high-risk NBL.

Poster presentation

Concurrent administration of temozolomide/irinotecan with dinotuxumab-beta for patients with relapsed/recurrent high-risk neuroblastoma: preliminary results of the national registry of the Hellenic Society of Pediatric Hematology/Oncology (HESPHO)

Clinical research

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ABSTRACT

Background and aims

The co-administration of Temozolomide iv/po and Irinotecan iv (TemIri) with anti-GD2 monoclonal antibody dinotuxumab-beta (DB) D1–5 has given promising results in children with high-risk neuroblastoma (NBL).

The aim of the present study is the description of the epidemiological, clinical characteristics and outcomes of the cohort of Greek patients with resistant or recurrent NBL who received TemIri/DB.

Methods

We retrospectively collected data from 13 patients in 5/7 Greek Oncology Departments.

Results

The median age of children at initial diagnosis was 3,03 years (0,12–8,55) with boys/girls' ratio 7/6. The 12/13 children had metastatic disease at diagnosis (bones 12, bone marrow 6). One infant initially presented as stage 4s (primary adrenal with liver metastases). N-MYC amplification was present in 3/13 children.

TemIri/DB therapy was administered in 4/13 children for resistant/significant residual disease and in 9/13 for recurrent NBL (5 for 1st; 2 for 2nd; 2 for 3rd relapse).

All children develop moderate toxicity, but dose interruption or modification has not been necessary in any case. The most common side effects were fever and hematological toxicity (13/13), diarrhea (7/13; 4/7 required Loperamide for symptom control), pain (4/13) and electrolyte disturbances (4/13).

Patients received 2 – 10 cycles each (median: 5,5). Two children develop disease progression/ relapse on TemIri/DB, 5/10 achieved complete remission, 2/10 partial, 2/10 very good partial remission and 2/10 stable disease. Four children following TemIri/DB received other treatments: ^{131}I-MIBG (2), surgery (1), cyclophosphamide/topotecan (1). Eleven children are alive: six on treatment, 3 with resistant disease, 1 in VGPR and 1 in CR3 for a median of 8.7 months (3.3-16.7), whilst two children have succumbed to NBL.

Conclusions

Immuno-chemotherapy with Temozolomide/Irinotecan and dinutuximab-beta appears to be an effective treatment for children with recurrent/resistant neuroblastoma. Toxicity is tolerable and manageable with the appropriate supportive therapy. The encouraging efficiency results in conjunction with the acceptable toxicity profile make this immune-chemotherapy regimen a promising single treatment or a bridging therapy in the management of recurrent/resistant high-risk NBL patients.

Poster presentation

BEST POSTER PRESENTATION AWARD AMG 2023

Identifying synergistic combinations with the BCL2 inhibitor venetoclax for high-risk neuroblastoma

Basic Research

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ABSTRACT

Background and aims

High-risk neuroblastoma (HR-NB) has one of the lowest survival rates of all paediatric cancers accounting for 15% of all paediatric cancer deaths with 60% of patients relapsing. BCL2 inhibitor venetoclax, in combination with cyclophosphamide and topotecan, has shown promising activity in an early phase trial in HR-NB patients and is a recurrent recommendation from the Australian child cancer personalised medicine trial, Zero Childhood Cancer (NCT03336931). However, this combination is limited by myelosuppression with continuous dosing. We aim to identify more effective and better tolerable venetoclax combinations using unbiased high-throughput screening and *in vivo* testing using patient-derived xenograft (PDX) models.

Methods

Co-immunoprecipitation was used to identify PDX models with low, intermediate, and high levels of Bim-BCL2 protein complex, a putative biomarker of venetoclax sensitivity. Combination drug screening was conducted *ex vivo* in three freshly dissociated PDX models with varying level of Bim-BCL2 complex using the IC30 concentration of venetoclax with a library of >120 approved oncology drugs (0.5nM–5μM) enriched for agents with paediatric safety data. Synergistic combinations were tested for tolerability in NSG mice, and then for efficacy in the PDX models in vivo, using schedules approximating those achievable in patients.

Results

Drugs synergistic with venetoclax in combination screens included conventional chemotherapies (DNA topoisomerase and microtubule inhibitors) and targeted agents (PARP, HDAC and AURKA inhibitors). Three combinations have so far been assessed in xenograft models. Vincristine-venetoclax prolonged survival in all models tested, while vorinostat-venetoclax had limited efficacy. The most effective combination, alisertib-venetoclax, elicited complete responses in all models, and outperformed venetoclax-cyclophosphamide-topotecan in one model in which studies have been completed. Furthermore, Bim-BCL2 protein complex levels predicted *in vivo* response to venetoclax. Additional combinations are undergoing testing. We will further assess promising combinations using less myelosuppressive discontinuous dosing schedules that are more clinically relevant and will test efficacy across of panel of HR-NB PDX models using clinical trial-like (n=1) experimental designs.

Conclusion

Systematic preclinical testing can be utilised effectively to identify the most synergistic venetoclax combination. Alisertib-venetoclax is a highly promising combination based on preclinical studies and should be considered for early-phase clinical trials.

Poster presentation

Vascular encasement image defined risk factors independently predict surgical complications in neuroblastoma

Clinical research

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ABSTRACT

Background and Aims

Specific Image Defined Risk Factors (IDRF) immediately prior to surgery may be more relevant to the paediatric oncology surgeon than simply the presence of any IDRF at diagnosis. The aim of this study was to determine the types IDRFs that independently predict postoperative complications.

Methods

We searched the New Zealand Children's Cancer Registry for all cases of neuroblastoma treated at a single paediatric oncology centre between January 2007 – February 2021 and determined the IDRF status on axial imaging at diagnosis and after neoadjuvant therapy. Surgical complications were scored by Clavien-Dindo grade and correlated with the total number of IDRFs (pre- and post-chemotherapy), and with the subset of vascular encasement IDRFs.

Results

Of 101 patients, 73 underwent surgical resection, and 32 (43.2%) had a surgical complication. Of the 55 IDRF-positive tumours, all were treated by neoadjuvant therapy, and in 17 all IDRFs resolved. Complications correlated with the number of post-neoadjuvant therapy vascular encasement IDRFs at OR 1.2 (95%CI 1.0 – 1.4, p = 0.03) and extensive IDRFs at OR 1.7 (95% CI 1.1 – 2.5, p = 0.02). Pre-chemotherapy IDRF status was not independently associated with complications when controlling for post-neoadjuvant therapy IDRF status. We report three cases of chyle leak associated with tumours encasing the origin of the celiac axis or the superior mesenteric artery.

Conclusions

The vascular encasement and extensive subtypes of IDRF are more useful prognostic indicators of surgical complications than the total number of IDRFs. This has implications for the reporting of IDRF status on pre-operative axial imaging and on surgical planning.

Oral presentation

T cell mediated killing of neuroblastoma is inhibited by secreted MDK and MIF

Basic research

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ABSTRACT

Background and aims

CAR-T cell therapy holds great promise for neuroblastoma. However, neuroblastoma tumours can escape T cell-mediated killing by, among others, inhibition of T cell activation through secreted immunosuppressive factors. Here, we aim to identify immunosuppressive factors which are secreted by neuroblastoma tumours and could be targeted to improve CAR-T cell efficacy.

Methods

To study immunoregulatory interactions in neuroblastoma, single-cell RNA-sequencing (scRNA-seq) data from 25 tumours were analysed using the CEL-seq2 platform. Interactions between tumour and immune cells were predicted using an unbiased ligand-receptor interaction analysis with CellChat. Proteins secreted by tumour cells (secretome) were analysed by mass spectrometry (LC-MS) on conditioned medium of patient-derived organoid cultures. The conditioned medium was concentrated using 3kDa Millipore filters and prepared for LC-MS. LC-MS data were acquired in data-dependent acquisition mode. The immunosuppressive capacity of neuroblastoma organoids was determined by flow cytometry readout of T cell proliferation and activation after incubation with concentrated secretome.

Results

ScRNA-seq analysis of 25 neuroblastomas showed that expression of two soluble factors, midkine (MDK) and Macrophage Migration Inhibitory Factor (MIF), was predicted to interact with tumour-infiltrating T cells, and correlated negatively with the cytotoxic potential of $CD8^+$ T cells. In bulk RNA-seq data of 498 neuroblastoma tumours (SEQC cohort) higher expression of MDK and MIF was significantly associated with worse event-free survival. In neuroblastoma organoid models, MDK and MIF were both among the top 100 most abundantly secreted proteins as assessed by LC-MS, indicating their potentially high levels in tumours. Functionally, recombinant MDK and MIF suppressed activation and cytotoxicity of healthy donor T cells *in vitro*. To assess the potential for therapeutic intervention, we pre-treated neuroblastoma organoids with a MIF-degrading PROTAC *in vitro*, which significantly reduced MIF secretion and significantly increased subsequent CAR-T cell activation in co-cultures, demonstrating the therapeutic potential of this approach.

Conclusions

We identified MDK and MIF as potent immunosuppressive factors in neuroblastoma using various unbiased analysis methods. MDK and MIF proved promising new targets for immunotherapy in neuroblastoma. Interventions targeting MIF and/or MDK may enhance the efficacy of CAR-T cell therapies in neuroblastoma, which we are currently further exploring as a therapeutic strategy.

Poster presentation

Neuroblastoma is associated with alterations in gut microbiome composition subsequent to maternal microbial seeding

Clinical research

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ABSTRACT

Background and aims
An altered gut microbiome composition has been linked to multiple cancer types, and reported in murine models of neuroblastoma. Whether children with neuroblastoma display alterations in gut microbiome composition remains unexplored.

Methods

We assessed gut microbiome composition by shotgun metagenomic profiling in an observational study on 288 individuals, consisting of patients with a diagnosis of neuroblastoma at disease onset (N=63), healthy controls matching the patients on the main covariates of microbiome composition (N=94), healthy siblings of the patients (N=13), mothers of patients (N=59), and mothers of the controls (N=59). We examined taxonomic and functional microbiome composition and mother-infant strain transmission patterns.

Results

Patients with neuroblastoma displayed alterations in gut microbiome composition characterized by reduced microbiome richness, decreased relative abundances of 18 species (including *Phocaeicola dorei* and *Bifidobacterium bifidum*), enriched protein fermentation and reduced carbohydrate fermentation potential. Using machine learning, we could successfully discriminate patients from controls (AUC = 82%). Healthy siblings did not display such alterations but resembled the healthy control group. No significant differences in maternal microbiome composition nor mother-to-offspring transmission were detected.

Conclusions

Patients with neuroblastoma display alterations in taxonomic and functional gut microbiome composition, which cannot be traced to differential maternal seeding. Follow-up research should include investigating potential causal links.

Poster presentation

Optimising ^{123}I-MIBG SUV measurements in neuroblastoma

Clinical research

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ABSTRACT

Background and Aims

Absolute quantification of ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) offers the potential to strongly enhance existing disease response measures, such as the International Neuroblastoma Response Criteria (INRC). However, practices vary significantly across centres and standardised techniques for quantitative SPECT/CT have yet to be established. To this end we present a clinical audit of physiological liver uptake in neuroblastoma patients, performed using locally optimised quantitative SPECT/CT reconstruction parameters.

Methods

Reconstruction parameters were optimised for the desired quantitative measurements using NEMA phantom studies. 50 multi-FOV ^{123}I-MIBG SPECT/CT scans of neuroblastoma patients were then reconstructed using the optimised parameters. All scans were acquired on a Siemens Intevo 16 SPECT/CT scanner and reconstructed with Hermes SUV SPECT software. Within each scan, 22mm diameter spherical Volumes of Interest (VOIs) were placed in the left and right lobes of liver and absolute activity concentrations were extracted. Absolute concentrations were rescaled into Standard Uptake Values (SUVs) scaled to body weight (SUV/BW), body surface area (SUV/BSA) and paediatric lean body mass (SUV/LBM). Liver uptake measurements were then compared on an intra- and inter-patient basis across both lobes and all measurement units.

Results

The right lobe of liver was found to provide more consistent uptake than the left lobe. Uptake measurements expressed as SUV/BW showed excellent agreement with previously published quantitative data. SUV/LBM was shown to be the most consistent measurement unit on both an intra- and inter-patient basis. A right lobe normal range of 0.5-2.1 SUV/LBM and a 95% right lobe standard deviation limit of 0.2 SUV/LBM were derived and are suggested as reference values.

Conclusions

Reliable absolute quantification of **^{123}I-MIBG SPECT/CT is feasible provided that reconstruction parameters are suitably optimised for the intended measurements. Liver SUV is most reliably measured in the right lobe and is least variable when measured using SUV/LBM. Liver uptake and variability may provide useful quality indicators** for quantitative ^{123}I-MIBG SPECT/CT **and should be collected alongside tumour SUV measurements.**

case presentations

Poster presentation

Dinutuximab beta combined with chemotherapy in a patient with recurrent/refractory neuroblastoma: a case report from the Children hospital, Anna Meyer, Florence (Italy)

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ABSTRACT

Background

The management of patients with recurrent/refractory neuroblastoma (R/R NB) depends on timing and nature of the relapse, prior therapy, tumor biology and patient's health. The combination of immunotherapy and chemotherapy may be a suitable treatment option and promising results were shown in the randomized phase II COG trial ANBL1221. We report the use of Dinutuximab beta in association with conventional chemotherapy (temozolomide-irinotecan) in a patient with R/R NB.

Case description

Male, 6 years, Ukrainian war refugee, R/R neuroblastoma (uncertain medical history). CT- guided tumor biopsy was performed: Neuroblastoma, MYCN non-amplified. In the first Whole Exome Sequencing (WES): mute genomic profile. He underwent 3 courses of conventional chemotherapy (temozolomide-irinotecan) achieving stable disease. After 3 further courses of temozolomide-irinotecan, a progressive disease was observed. The combination of temozolomide-irinotecan and anti-GD2 was planned. Dinutuximab beta was given as continuous long-term infusion of 10 mg/m^2/day on days 2-6 of each 21-day course. Chemotherapy was given on days 1-5 of each course. Tumor response was evaluated after 2^{nd} and 5^{th} course with a stable disease and no toxicity occurred. No dinutuximab beta dose reductions were required and the patient underwent the 6. course. In the 2^{nd} WES: mutation in the NF1 gene, targeted by sirolimus. A target therapy with sirolimus in combination with conventional chemotherapy could be a chance to reach a long remission period.

Conclusion

The combination therapy with dinutuximab beta and temozolomide-irinotecan in our patient heavily pre-treated was well tolerated and stabilized the disease. Moreover, it allowed to gain time and re-test genomic profile to seek molecularly targeted therapy. A tailored treatment plan of chemo-immunotherapy combination is a hopeful treatment option to achieve a stable disease prioritizing the quality of life and limiting severe adverse events.

Oral presentation

Early-onset busulfan-induced lung injury in two patients with high-risk neuroblastoma after autologous stem cell transplantation

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ABSTRACT

Background and aims

Pulmonary toxicity is a rare but serious well known side effect of Busulfan, a key anticancer agent used in first-line therapy of high-risk neuroblastoma. We here report the clinical and radiographic features of Busulfan-induced lung injury and the clinical management of two patients with high-risk neuroblastoma.

Clinical cases

Patient 1 developed a partial respiratory impairment with dyspnea and continuous low-level oxygen need 40 days after i.v. busulfan application according to the GPOH NB2017 Guidance. Symptoms fully resolved after 5 months of topical treatment with inhalation corticosteroids and short-acting b-agonists combined with azithromycin and systemic low-dose corticosteroid treatment. Serial CT-based imaging showed atypical pneumonic changes with ground glass opacities that resolved without evidence of evolving pulmonary fibrosis. During partial respiratory insufficiency, antitumoral therapy consisted of a modified 4-compound RIST regimen. Standard of care maintenance therapy with dinutuximab beta was started after discontinuation of corticosteroid therapy and has been well tolerated.

One month prior to busulfan application, patient 2 had a Covid -9 infection without respiratory symptoms. Repeated PCRs from respiratory swabs documented negative tests for SARS-CoV2 virus for a total of three weeks prior to starting the busulfan/melphalan high-dose chemotherapy. Patient 2 developed 2 life-threatening acute pulmonary cytokine release syndromes on days 60 and 100 after i.v. busulfan application, requiring invasive ventilation followed by prolonged non-invasive ventilation. Despite intensified immunosuppressive therapy with methylprednisolone pulses and extracorporal photopheresis in addition to the therapeutic measures described above, patient 2 continues to require intensive care measures. The CT scans show undulating changes with diffuse intra-alveolar and interstitial patterns. To delay the progression to long-lasting damage, therapy with the small molecule tyrosine kinase inhibitor nintedanib was initiated.

Conclusions

The application of busulfan-based high-dose chemotherapy can elicit serious not yet fully understood pulmonary toxicity in individual patients. Symptoms and signs of busulfan-mediated lung injury are nonspecific and difficult to differentiate from changes caused by other drugs and/or infections. The individual toxicities described here underline the importance of real time busulfan drug monitoring with individual dose adjustments and support continuous monitoring for respiratory viruses as potential co-founders for lung toxicity.

Poster presentation

Combination of radionuclide therapies in pediatric neuroblastoma: A case report

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ABSTRACT

Case Summary

An 8 year old girl with no previous history of any known disease presented with complaints of abdominal and low back pain for 4-5 months. MRI performed due to increased complaints and numbness in the left leg revealed an intradural extramedullary mass located in the spinal canal with prediagnosis of ependymoma narrowing the spinal cord. 10 x 7.5 cm mass lesion in the left upper quadrant and intraabdominal lymphadenopathies were detected at abdominal MRI. Bone marrow biopsy was performed with a prediagnosis of neuroblastoma and normocellular bone marrow showing neuroblastoma metastasis. The mass at Th12 level was found to be neuroblastoma (poor in shwannian stroma) with a differentiation percentage of <5% (N-MYC mutation negative). A9 and A11 chemotherapy protocols was administered and continued after the biopsy. After 3 cycles of chemotherapy, surgery was performed - 7 cm mass in the left suprarenal space was excised. The biopsy result was ganglioneuroblastoma. Postoperative abdominal MRI and I^{123} MIBG SPECT/CT showed residual tumor tissue in left suprarenal space. I^{123} MIBG SPECT/CT imaging was performed 2 months later and the foci in the anterior of the operation lobe and right psoas muscle were found to be malignant. I^{131} MIBG treatment was not applied because of insufficient receptor uptake. Curative radiotherapy was planned. Filgrastim treatment and

bone marrow transplantation were planned and then the 2nd ICE protocol was started (not eligible for autologous bone marrow transplantation). After 4 cycles, it was planned to stop the chemotherapy. Ga^{68} DOTATE PET/CT and I^{123} MIBG SPECT/CT imaging was performed, it was deemed appropriate to aply Lu^{177} DOTATE therapy. Patient received 4 cycles in 8 weeks intervals. Lu^{177} of 80 mci was administered in each cycle. 5th cycle was postponed due to general condition disorder and thrombocytopenia (75 10^3/uL). Control imaging was performed with I^{123} MIBG and Ga^{68} DOTATE and nearly 35% regression was observed. After the general condition of the patient improved, 2 more cycle of treatment were given and it was decided to excise the primary lesion as it remained stable on control imaging. After operation 1 cycle of 80 mci Lu^{177} and 1 cycle TOPG chemotherapy was applied. After these protocols, the patient developed opportunistic pathogen infection and hemorrhagic foci developed in the brain. After her general condition improved, 2nd cycle of 80 mci Lu^{177} therapy was applied. I^{123} MIBG SPECT/CT was performed for control purposes and response of the lesions to treatment was evaluated as mixed. We decided to switch to a new chemotherapy protocol (TVD).

Oral presentation

Resistant progressive ganglioneuroblastoma and newer treatment modalities

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ABSTRACT

Background and aims

High-risk neuroblastoma based on the INRGSS system is a tumor of extremely high malignancy, and therapeutic interventions are challenging. About half of patients diagnosed with neuroblastoma are classified as high-risk. This group continues to have poor cure rates despite multiagent chemotherapy, surgery, high-dose chemotherapy with autologous stem cell rescue, radiotherapy and immunotherapy directed against GD2. Current efforts to improve the outcome of patients with newly diagnosed disease include incorporating new targeted therapies earlier in the course of the disease. ALK gene mutations or gene amplifications have been identified in up to 15% of newly-diagnosed high-risk neuroblastomas.

Purpose

To present a patient with resistant metastatic ganglioneuroblastoma and the newest treatments.

Methods

A 22-month-old girl with metastatic ganglioneuroblastoma was diagnosed after chronic diarrhea, with an intra-abdominal tumor measuring 7.4 x 3.9 x 6.5 cm. Biopsy findings revealed nodular ganglioneuroblastoma with favorable features (MKI 2%), MYCN (-). Later-date screen revealed ALK mutation p.I1170N. In MIBG the localizations of the disease were: skull, facial bones, abdomen, femur, shins, humerus, and pelvis. Because of the low MKI, a focal skull biopsy was performed, which had the same histological pattern confirming the diagnosis. She received Rapid-COJEC induction chemotherapy on the SIOPEN HR NBL2 protocol following randomization. Post-induction staging revealed 2 new MIBG avid foci.

Results

Due to disease progression at the end of induction, she received modified VERITAS protocol, including temozolomide-irinotecan (TEMIRI), with early administration of dinutuximab-beta. She then proceeded to 2 ^{131}MIBG infusions (final exposure 3.8 Gy) and first ASCT with a partial remission. Due to ALK positivity, Lorlatinib is prescribed awaiting BuMel MAT.

Conclusions

The newest treatment approaches in treating high-risk neuroblastoma involves incorporating complex protocols to overcome post-induction relapsed/refractory disease. The identification of newer tumor targets and novel immunotherapies could improve outcomes and clinical trials for regimens designed to target individual genetic aberrations are ongoing. More studies are needed to find the optimal treatment approaches. Combination treatments including chemo-immunotherapies, targeted treatments, new agents, tandem transplants, and aggressive local treatment are under study to improve survival and cure rates for high-risk neuroblastoma.

Oral presentation

Combined ALK and RAS/MAPK mutation in a patient with refractory neuroblastoma and a left iliac bone lesion: for ALK inhibitor or not?

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ABSTRACT

Case Presentation

A 6 year old girl diagnosed with high risk neuroblastoma outside the UK was referred to our center for further treatment.

She presented with paraplegia and had 3 cycles of COG ANBL0532 chemotherapy. Review of histology from bone marrow confirmed the diagnosis of poorly differentiated neuroblastoma, unfavorable histology with low MKI. Cytogenetics was not performed due to inadequate sampling. Staging showed a large right suprarenal primary tumour with widespread mIBG avid bone metastasis (SIOPEN score 44), bone marrow, nodal and skull based dural disease. She completed 6 cycles of the COG induction regimen and peripheral blood stem cell harvest was carried out. Reassessment showed primary tumour response, bone marrow complete response but more than 10 sites of bone disease. Therefore second line chemotherapy with Bevacizumab, Irinotecan and Temozolomide(BIT) was commenced. Following 2nd and 4th cycles, reassessment indicated further improvement.

However, following 6th cycle of BIT, a new left iliac bony disease was found. Therapy was changed to temozolomide and irinotecan with GD2 antibody. After 2 cycles, reassessment showed progressive mIBG avid disease at the left iliac bone but none elsewhere. Biopsy of this lesion confirmed *MYCN* amplificated neuroblastoma. Numerous segmental chromosomal changes were detected from SNP array, including 11q loss,17q gain, *TERT* gain and *PTPRD* loss. NGS panel also identified driver variants of *ALK* and *HRAS.* High dose palliative radiotherapy (20Gy) was given to this site and systemic therapy changed to temozolomide and topotecan with GD2 antibody as per BEACON study. After 3 cycles, mIBG uptake increased at the left iliac bone and relatively static appearance elsewhere with SIOPEN score 7. Primary tumour resection was carried out and showed mostly necrosis. She is planning to be given high dose chemotherapy.

Educational Point

Deletions of *PTPRD* gene and gains of *TERT* gene have been previously reported and driver variants in the *RAS/MAPK* pathway are frequent findings in relapsed neuroblastoma. RAS/MAPK pathway mutations in addition to *ALK* have been reported to confer resistance to 3rd generation ALK inhibitors such as lorlatinib.

Questions

Should we consider this as progressive disease? Can we still achieve cure? Should we give a 1st or 2nd generation ALK inhibitor with a MEK inhibitor?

Poster presentation

Experiences with dinutuximab beta treatment in pediatric high-risk neuroblastoma cases

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ABSTRACT

Backround

Despite recent advances high-risk neuroblastoma still has a high mortality rate. Treatment includes chemotherapy, radiotherapy, bone marrow transplantation and immunotherapy. Previously, maintenance therapy for high-risk patients included retinoic acid treatment in Hungary, but from 2018 dinutuximab beta treatment became available. Dinutuxumab beta is a chimeric monoclonal antibody targeting the disialo-ganglioside 2 (GD2) molecule on neuroblastoma cells. In our centre dinutuximab beta was introduced in August 2022 as part of the maintenance treatment. Therefore, our aim was to retrospectively analyse our data with a focus on response, side effect profile and tolerability.

Results

Between 2021 and 2023, we treated 8 neuroblastoma patients, 4 of whom were diagnosed with high-risk neuroblastoma. They received dinutuximab beta therapy combined with retinoic acid as part of their maintenance treatment. All children were classified as stage 4 according to INSS criteria, 1 case was confirmed to have N-MYC amplification and all our patients had initial bone marrow involvement. The therapeutic response was assessed by imaging studies, pathological analysis and flowcytometry analysis of bone marrow. All children received induction and consolidation therapy according to the HR-NBL 1.8 protocol before dinutuximab beta treatment. No child achieved complete remission before immunotherapy. Dinutuximab was administered with supportive anti-allergic and analgesic therapy. Two children completed five 35-day cycles according to the protocol, one patient achieved complete remission, the other patient showed partial remission.

Dinutuximab treatment of 2 children is still ongoing with satisfactory interim response. No serious adverse events were observed. One patient developed hypotension as part of capillary leak syndrome during the first cycle that ceased spontaneously. All children experienced mild oedema, diarrhoea and hypokalaemia, which responded well to conservative treatment.

Conclusions

Our experiences confirm that dinutuximab treatment is well tolerated without any serious side effects. Standardization of dinutuximab beta application in maintenance therapy of high-risk neuroblastoma patients may significantly improve survival.

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QARZIBA® is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures.[1]

In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, QARZIBA® should be combined with interleukin-2 (IL-2).[1]

Footnote
*Partial response or better to treatment prior to immunotherapy.

References

1. QARZIBA® (dinutuximab beta). Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/qarziba-epar-product-information_en.pdf. Accessed September 2023.
2. Ladenstein R, et al. Lancet Oncol. 2018; 19(12): 1617–1629.

Adverse reporting can be found on the next page.

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ABBREVIATED PRESCRIBING INFORMATION – Qarziba ▼ (dinutuximab beta). Before prescribing Qarziba please refer to full Summary of Product Characteristics. **Presentation:** Concentrate for solution for infusion containing 20 mg dinutuximab beta. **Indication:** For the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures. In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, Qarziba should be combined with interleukin-2 (IL-2). **Dosage & Administration:** Restricted to hospital-use only and must be administered under the supervision of a physician experienced in the use of oncological therapies. It must be administered by a healthcare professional prepared to manage severe allergic reactions including anaphylaxis in an environment where full resuscitation services are immediately available. Treatment consists of 5 consecutive courses, each course comprising 35 days. The individual dose is determined based on the body surface area and should be a total of 100 mg/m2 per course. Two modes of administration are possible: 1) continuous infusion over the first 10 days of each course (a total of 240 hours) at the daily dose of 10 mg/m2 or 2) five daily infusions of 20 mg/m^2 administered over 8 hours, on the first 5 days of each course. When IL-2 is combined with Qarziba, it should be administered as subcutaneous injections of 6×10^6 IU/m^2/day, for 2 periods of 5 consecutive days, resulting in an overall dose of 60×10^6 IU/m^2 per course. The first 5-day course should start 7 days prior to the first infusion of Qarziba and the second 5-day course should start concurrently with Qarziba infusion (days 1 to 5 of each Qarziba course). ***Paediatric population:*** The safety and efficacy of Qarziba in children aged less than 12 months have not yet been established. No data are available. ***Renal impairment:*** No data are available. ***Hepatic impairment:*** No data are available. ***Contraindications:*** Hypersensitivity to the active substance or to any of the excipients. Acute grade 3 or 4, or extensive chronic graft-versus-host disease (GvHD). **Special warnings and precautions for use:** ***Traceability:*** In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. ***Pain:*** Neuropathic pain usually occurs at the beginning of the treatment and premedication with analgesics, including intravenous opioids, prior to each infusion of Qarziba is required. A triple therapy, including nonopioid analgesics (according to WHO guidelines), gabapentin and opioids, is recommended for pain treatment. The individual dose may vary widely. ***Hypersensitivity reactions:*** Severe infusion-related reactions, including cytokine release syndrome (CRS), anaphylactic and hypersensitivity reactions, may occur despite the use of premedication. Occurrence of a severe infusion related reaction (including CRS) requires immediate discontinuation of Qarziba therapy and may necessitate emergency treatment. CRS frequently manifests itself within minutes to hours of initiating the first infusion and is characterised by systemic symptoms such as fever, hypotension and urticaria. Anaphylactic reactions may occur as early as within a few minutes of the first infusion with Qarziba and are commonly associated with bronchospasm and urticaria. ***Capillary leak syndrome (CLS):*** Usually develops within hours after initiation of treatment, while clinical symptoms (i.e. hypotension, tachycardia) are reported to occur after 2 to 12 hours. Careful monitoring of circulatory and respiratory function is required. ***Neurological disorders of the eye:*** May occur as Qarziba binds to optic nerve cells. No dose modification is necessary in the case of an impaired visual accommodation that is correctable with eye glasses, as long as this is judged to be tolerable. Treatment must be interrupted in patients who experience Grade 3 vision toxicity. In case of any eye problems, patients should be referred promptly to an ophthalmology specialist. Peripheral neuropathy: Occasional occurrences of peripheral neuropathy have been reported. Cases of motor or sensory neuropathy lasting more than 4 days must be evaluated and non- inflammatory causes, such as disease progression, infections, metabolic syndromes and concomitant medication, should be excluded. Treatment should be permanently discontinued in patients experiencing any objective prolonged weakness attributable to Qarziba administration. For patients with moderate (Grade 2) neuropathy (motor with or without sensory), treatment should be interrupted and may be resumed after neurologic symptoms resolve. ***Central neurotoxicity:*** Central neurotoxicity has been reported following treatment with Qarziba. If central neurotoxicity occurs the infusion should be interrupted immediately and the patient treated symptomatically, other influencing factors such as active infection, metastatic spread of neuroblastoma to central nervous system, neurotoxic concomitant medications should be ruled out.
Treatment with Qarziba should be permanently discontinued following the occurrence of severe neurotoxicity that includes Grade 3 or 4 central neurotoxicity with substantial prolonged neurological deficit without any detectable reason, recurrent grade 1-3 neurotoxicity and/or permanent neurological deficit and all grades of posterior reversible encephalopathy syndrome and transverse myelitis. ***Systemic infections:*** Patients are likely to be immunocompromised as a result of prior therapies as they typically have a central venous catheter in situ, they are at risk of developing systemic infection. Patients should have no evidence of systemic infection and any identified infection should be under control before starting therapy. ***Haematologic toxicities:*** Occurrence has been reported with Qarziba, such as erythropenia, thrombocytopenia or neutropenia. Grade 4 haematologic toxicities, improving to at least Grade 2 or baseline values by start of next treatment course, do not require dose modification. ***Laboratory abnormalities:*** Regular monitoring of liver function and electrolytes is recommended. **Interactions:** No studies performed. A risk for indirect reduction of CYP activity due to higher TNF-α and IL-6 levels and, therefore, interactions with concomitantly used medicinal products, cannot be excluded. ***Corticosteroids:*** Due to their immunosuppressive activity, concomitant treatment with corticosteroids is not recommended within 2 weeks prior to the first treatment course until 1 week after the last treatment course with Qarziba, except for life-threatening conditions. ***Vaccinations:*** Should be avoided during administration of Qarziba until 10 weeks after the last treatment course, due to immune stimulation through Qarziba and possible risk for rare neurological toxicities. ***Intravenous immunoglobulin:*** Concomitant use of intravenous immunoglobulins is not recommended as they may interfere with Qarziba-dependent cellular cytotoxicity. **Women of childbearing potential/contraception in males and females:** Qarziba should not be used in women of childbearing potential not using contraception. It is recommended that women of childbearing potential use contraception for 6 months after discontinuation of treatment with Qarziba.
Pregnancy: Qarziba should not be used during pregnancy. ***Breast-feeding*** – No data. Breast-feeding should be discontinued during treatment and for 6 months after the last dose. ***Fertility*** - Unknown. **Effects on ability to drive and use machines:** Qarziba has major influence on the ability to drive and use machines. Patients should not use or drive machines during treatment with Qarziba. **Side effects:** ***Very common (≥ 1/10)*** - infection (including pneumonia, skin infection, herpes virus infection, myelitis, encephalomyelitis), device related infection, anaemia, leukopenia, neutropenia, thrombocytopenia, hypersensitivity, cytokine release syndrome, fluid retention, headache, mydriasis, pupillotonia, eye oedema (eyelid, periorbital), tachycardia, hypotension, capillary leak syndrome, hypoxia, cough, vomiting, diarrhoea, constipation, stomatitis, pruritus, rash, urticaria, pyrexia, chills, pain (includes abdominal pain, pain in extremity, oropharyngeal pain, and back pain reported in >10% of patients. In addition, other common pain types reported were arthralgia, injection site pain, musculoskeletal pain, bone pain, chest pain, and neck pain), peripheral oedema, face oedema, increased weight, increased transaminases, increased gamma glutamyltransferase, increased blood bilirubin, increased blood creatinine. ***Common (≥ 1/100 to < 1/10)*** – sepsis, lymphopenia, anaphylactic reaction, decreased appetite, hypoalbuminaemia, hyponatraemia, hypokalaemia, hypophosphataemia, hypomagnesaemia, hypocalcaemia, dehydration, agitation, anxiety, peripheral neuropathy, seizure, paraesthesia, dizziness, tremor, ophthalmoplegia, papilloedema, accommodation disorder, blurred vision, photophobia, cardiac failure, left ventricular dysfunction, pericardial effusion, hypertension, bronchospasm, dyspnoea, respiratory failure, lung infiltration, pulmonary oedema, pleural effusion, tachypnoea, laryngospasm, nausea, lip oedema, ascites, abdominal distension, ileus, dry lips, dermatitis (including exfoliative), erythema, dry skin, hyperhidrosis, petechiae, photosensitivity reaction, muscle spasms, oliguria, urinary retention, hyperphosphaturia, haematuria, proteinuria, injection site reaction, decreased weight, decreased glomerular filtration rate, hypertriglyceridaemia, prolonged activated partial thromboplastin time, prolonged prothrombin time, prolonged thrombin time. ***Uncommon (≥ 1/1,000 to < 1/100)*** - disseminated intravascular coagulation, eosinophilia, serum sickness, intracranial pressure increased, posterior reversible encephalopathy syndrome, hypovolaemic shock, veno-occlusive disease, enterocolitis, hepatocellular injury, renal failure. **Packaging, quantity and price:** Glass vial containing 4.5 ml concentrate for solution for infusion. The pricing of Qarziba and associated reimbursement differs between countries. Please check with your local country for specific details. **Storage requirements:** ***Unopened vial*** - 4-year shelf-life. Store in a refrigerator (2°C – 8°C). Keep the vial in the outer carton in order to protect from light. ***In-use stability*** - demonstrated for up to 48 hours at 25°C (50 ml syringe) and for up to 7 days at 37°C (250 ml infusion bag), after cumulative storage in a refrigerator (2°C – 8°C) for 72 hours. From a microbiological point of view, the product should be used immediately. **Legal Category:** POM. **Marketing Authorisation Number:** EU/1/17/1191/001. Full prescribing information, including the SmPC, is available from the **Marketing Authorisation Holder:** Recordati Netherlands B.V., Beechavenue 54, 1119PW, Schiphol-Rijk, Netherlands **Date of preparation:** July 2023 – GL-QAR-0001

▼ This medicine is subject to additional monitoring. Adverse events should be reported as per local regulatory authorities' requirements. Adverse events should also be reported to EUSA Pharma at safety@eusapharma.com.

GL-DNB-2300049 | September 2023

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