European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

Refractory high-risk neuroblastoma management

Presenter: Alba Rubio
Expert: Ruth Ladenstein
Moderator: Teresa de Rojas

ERN PaedCan – Young SIOPE webinar series

"Most challenging cases in paediatric oncology"

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COI Declaration

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Alba Rubio:

My institution (not me) receives funding for conducting industry-sponsored clinical trials

Ruth Ladenstein:

Honoraria	Consulting or Advisory Role	Expert Testimony	Travel, Accommodations, Expenses
Apeiron Biologics	Apeiron Biologics	Apeiron Biologics	Apeiron Biologics
Boehringer Ingelheim	Boehringer Ingelheim		
EUSA Pharma		EUSA Pharma	EUSA Pharma

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Clinical case

July/2017

Eight-year-old boy presented to the ED with fatigue and pain in extremities for the past 2 months.

No relevant past medical history

Physical exam:

HR 100 bpm, BP 110/50 mmHg, RR 20 bpm, temp 36ºC
Abdominal mass in the right hemiabdomen of 8 cm in the longest diameter.
No other findings

Blood test: Hb 10g/dl, WCs 8600/mcl, platelets 370000/mcl. U&E, LTS normal. ESR 54mm/h. Negative serological tests.

Chest x-ray: Normal

Abdominal MRI:

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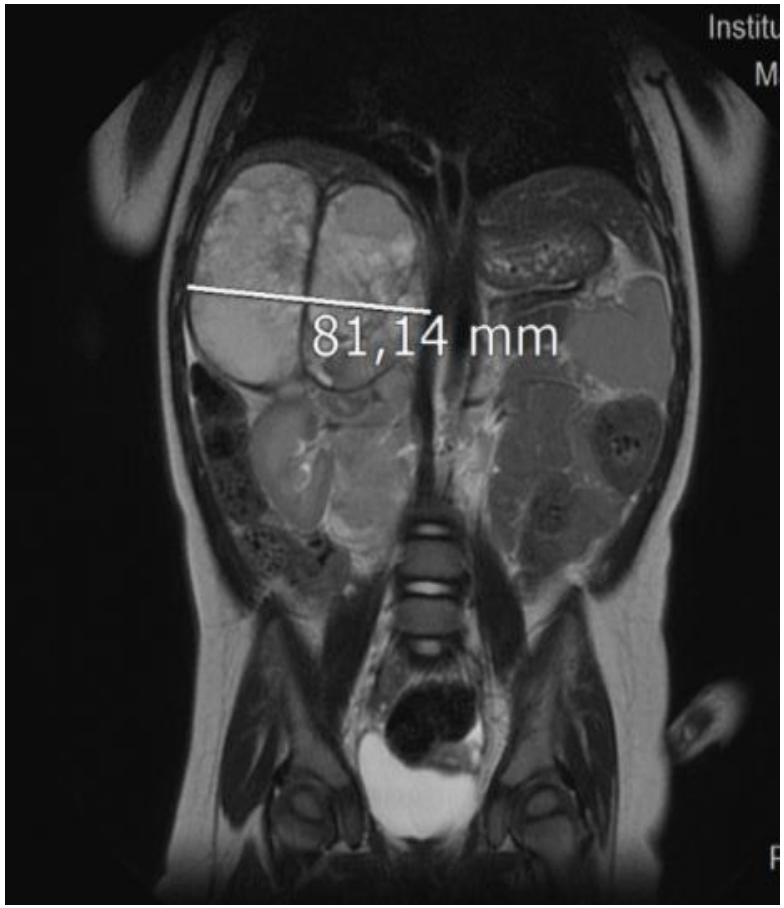

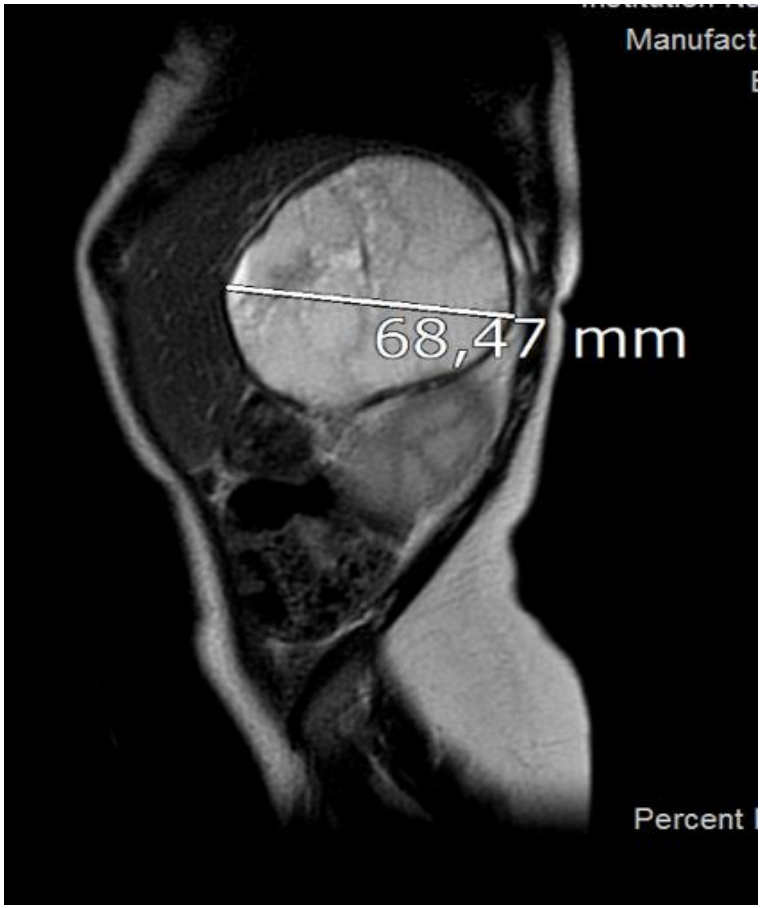

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Echo-guided biopsy:

- Pathology report:

Morphology: Undifferentiated neuroblastoma. IHC: PHOX2B and synaptophysin +, CD99 and CD45 -.

FISH: NMYC not amplificated.

SNP array–based karyotyping: No segmental chromosome alterations.

NGS ALK: no mutated.

- **MIBG study:** Numerous affected bones including the skull, several vertebrae, the right and left femur and iliac bones (SIOPEN score 33)

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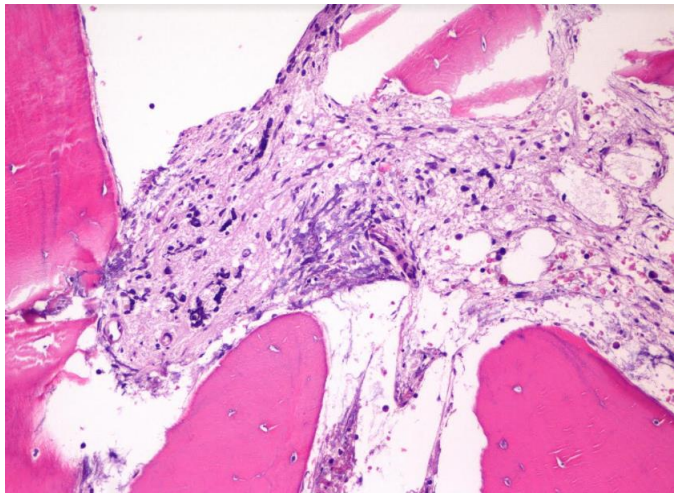
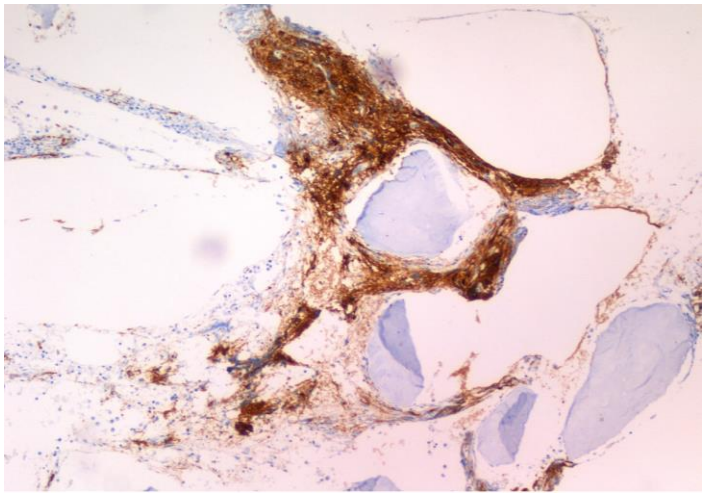
- **Bilateral bone marrow:** consistent with neuroblastoma infiltration
  Morphology: Small, round, blue cell separated by a fibrillar matrix
  Immunohistochemistry: PHOX2B and synaptophysin +



Hematoxylin and eosin 20x



Synaptophysin 10x

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The patient was diagnosed with **neuroblastoma**

- Primary tumour: Right adrenal gland
- Metastasis: Ganglia, bone marrow and bones

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Question 1

According to the International Neuroblastoma Risk Group Staging System (INRGSS) how do you classify this patient?

1. High risk
2. Intermediate risk
3. It is mandatory to know the chromosome aberrations in copy number (ploidy) to classify it
4. It depends on the primary tumour extent of resection

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- **Starts treatment according to HR-NBL1/SIOPEN protocol**

- COJEC induction 28/Jul- 15/Oct/2017

	Dose /day	days	days	days	days	days	days	days	days
G-CSF	5µg/kg	3 - 8 ⇔	12-18 ⇔	23-28 ⇔	32- 38 ⇔	43- 48 ⇔	52-58 ⇔	63-68 ⇔	72 till ⇔ harvest
CBDCA	750mg/m²	⇩				⇩			
Vp16	175mg/m²	⇩⇩		⇩⇩		⇩⇩		⇩⇩	
VCR	1.5mg/m²	⇩	⇩	⇩	⇩	⇩	⇩	⇩	⇩
CDDP	80mg/m²		⇘ctn		⇘ ctn		⇘ ctn		⇘ ctn
CYC	1050mg/m²			⇩⇩				⇩⇩	

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- **Starts treatment according to HR-NBL1/SIOPEN protocol**

- **COJEC induction 28/Jul- 15/Oct/2017**

After COJEC:
Primary tumour assessment: No response
Metastatic disease assessment: No response

} Refractory disease

- **Primary tumour surgery: 02/Nov/2017**

After surgery:
Primary tumour assessment: Complete resection
Metastatic disease assessment: Unchanged

- **Stem cells are collected via periphery harvest for 2 transplants: 20/Nov/2017**

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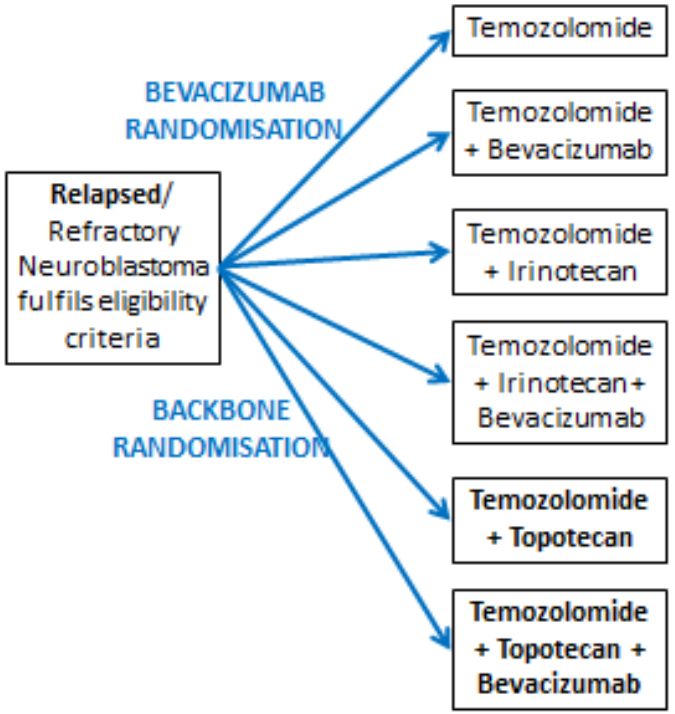
- **Start 2º line scheme in BEACON 1 trial**

6 cycles of (28/Nov/2017-20/May/2018):

bevacizumab (10 mg/kg iv days +1, +15)
+
temozolomide (200mg/m2 po days 1-5)

Metastatic disease assessment
(each 2 cycles): Stable disease



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Question 2

What would you do in this patient at this point?

1. Treatment with immune check point inhibitors (ie. nivolumab)
2. Treatment with chemo-immunotherapy (ie. TOTEM+dinutuximab)
3. Continue with BUMEL transplantation according to HR-NBL protocol.
4. MIBG therapy

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22/Jun/2018 **131I-mIBG therapy according to VERITAS protocol**

- First dose: 131I-mIBG (370mCi) 22/Jun/2018 + topotecan (0,7mg/m2/day) 22-26/Jun/2018
- Second dose: 131I-mIBG (110mCi until a total whole-body radiation dose of 4 Gy) 07/Jul/2018 + topotecan (0,7mg/m2/day) 07-11/Jul/2018
- Autologous stem-cell infusion 20/Jul/2018

Metastatic disease assessment: Partial response (no ganglia and no BM disease, only persistence of 4 points of bone disease in the right and left iliac bones and right proximal femur)

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10/Sept/2018 **BUMEL autologous HSCT**

- Metastatic disease assessment: Unchanged (persistence of 4 points of bone disease)

Radiotherapy in primary tumour bed Nov/2018 (21 Gy)

Maintenance with ch14.18/CHO + isotretinoin according to HR-NBL1/SIOPEN protocol between Jan-Jul/2019

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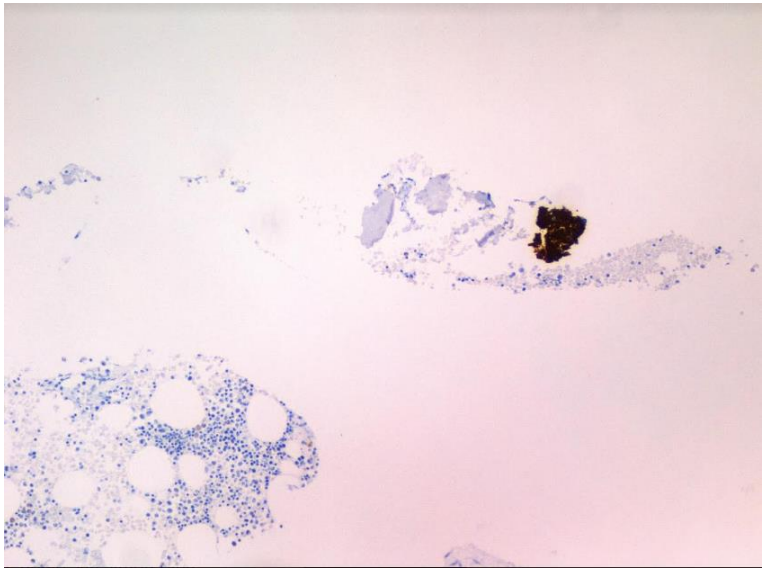
EOT assessments (Aug/2019) showed disappearance of all bone lesions but presence of isolated neuroblastoma cells in one right bone marrow trephine biopsy



Synaptophysin 10x

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Question 3

What would you do in this patient at this point?

1. No treatment, wait and see
2. New line of treatment

We adopted a wait-and-see approach.

To date, one year and a half later, the disease remains stable, with no new lesions but with residual neuroblastoma in bone marrow eventually (different locations on right or left bone marrow).

Planning to send sample to reference lab for reviewing

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Discussion

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Which other approaches might have been helpful in this patient?

Which is the optimal timing for primary tumour resection in metastatic patients?

How should be prioritized all new different therapies in refractory/relapsed NB? (what, for whom and when?)

What is the meaning of residual tumour cells (in bone marrow or as tumour residual lesion or as an isolated MIBG uptake) at the EOT in patients with NB?

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Take-home messages

- Currently there are many new strategies for refractory/relapsed NB patients, which increase EFS and could increase OS (under clinical research)
- Difficulties in prioritize new therapies
- In case of doubts in tumour assessments, samples and images could be sent for reviewing in a reference site.