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for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

August 18th 2021

Alberto Romano & Sandra Strauss

"Treatment for chondrosarcoma in Li Fraumeni syndrome: what's next?"

Chair: Teresa de Rojas

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COI Declaration

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

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History

A 16 years old boy presented with a three month history of right hip pain and difficulty in walking.

He also reported the appearance of a swelling on the right hip for about a month.

Paracetamol, NSAIDs and steroids did not improve the pain.

He revealed that his mother at the age of 18 suffered for femoral osteosarcoma (treated with chemotherapy and surgery) and died at the age of 34 for breast cancer.

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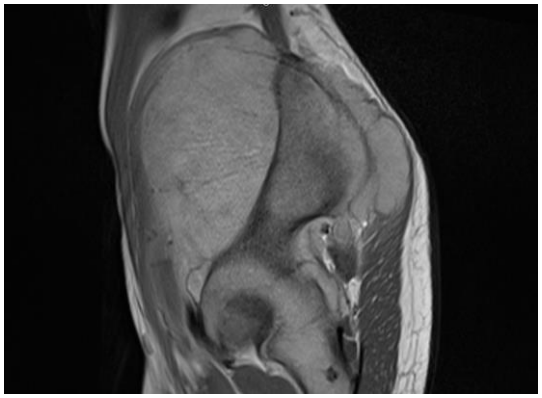
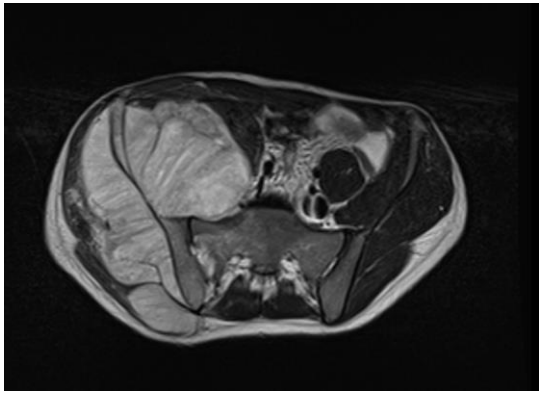
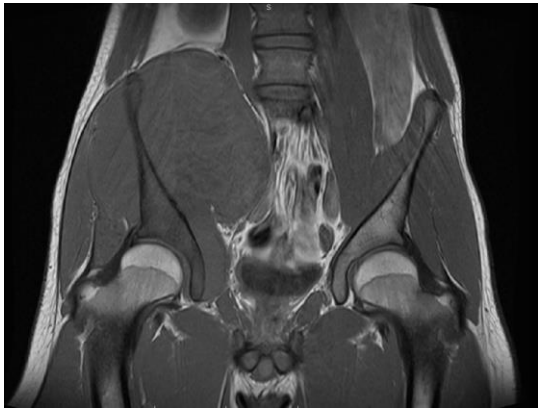
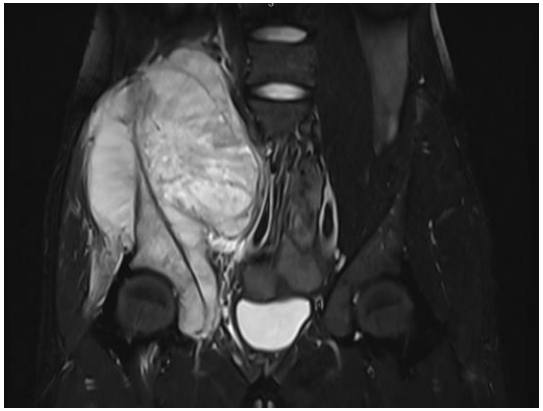
MRI

Soft tissue mass (ø 15 cm x 14 cm x 13 cm) hypointense in T1 and hyperintense in T2 between the muscles and right iliac bone.









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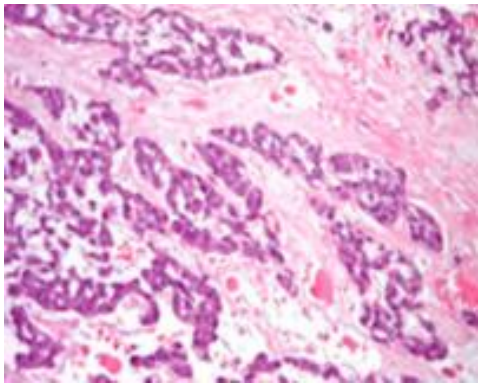
Histology

Myxoid mesenchymal neoplasm

Immunohistochemistry: absent expression of S100, synaptophysin, NSE, desmin, SMA, MyoD1, CD117, pan-CK, CD34 and STAT6

Presence of NR4A3 traslocation [EWSR1(ex7)/NR4A3(ex2)]



DIAGNOSIS: Extraskeletal myxoid chondrosarcoma (EMC)

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QUESTION 1

What investigations should be performed before starting the treatment?

- Total Body CT
- PET-CT
- Bone marrow aspiration and biopsy
- Genetic consultation
- All the answers

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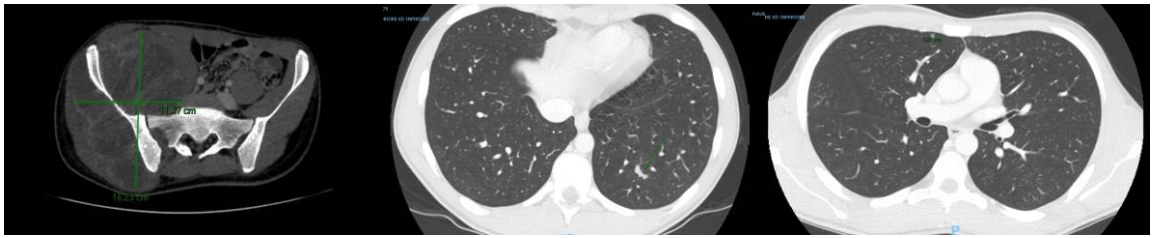
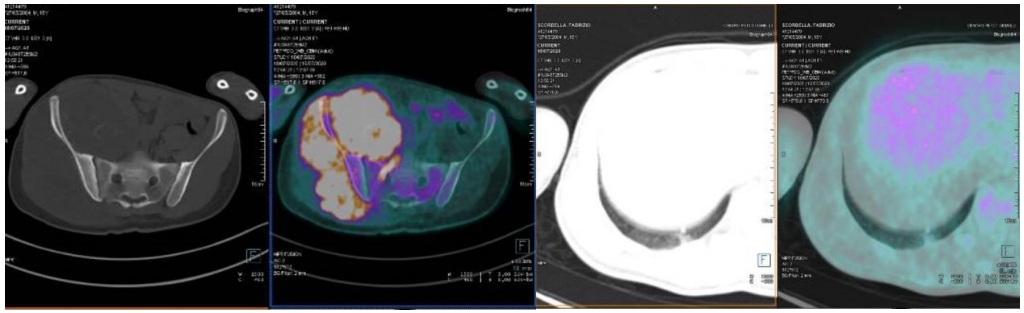
Patient assessment

- Total Body CT= multiple bilateral pulmonary micrometastasis



- PET-CT= elevated metabolic activity in the right pelvis and bilaterally in the lung



- Bone marrow aspiration and biopsy= (performed only on the left iliac spine due to the presence of the tumor around the right iliac spine) no metastasis

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Why genetic consultation?

Cancer patients who should be tested for germline disease-causing *TP53*[a]

Recommendation 1	All patients who meet the modified 'Chompret Criteria' should be tested for germline *TP53* variants: • *Familial presentation*: proband with a *TP53* core tumour (breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system tumour, adrenocortical carcinoma) before 46 years AND at least one first- or second-degree relative with a core tumour before 56 years; *or* • *Multiple primitive tumours*: proband with multiple tumours, including 2 *TP53* core tumours, the first of which occurred before 46 years, irrespective of family history; *or* • *Rare tumours*: patient with adrenocortical carcinoma, choroid plexus carcinoma, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history; *or* • *Very early-onset breast cancer*: Breast cancer before 31 years, irrespective of family history
Recommendation 2	Children and adolescents should be tested for germline *TP53* variants if presenting with: • Hypodiploid acute lymphoblastic leukaemia (ALL); *or* • Otherwise unexplained *sonic hedgehog*-driven medulloblastoma; *or* • Jaw osteosarcoma
Recommendation 3	Patients who develop a second primary tumour, within the radiotherapy field of a first core *TP53* tumour which occurred before 46 years, should be tested for germline *TP53* variants
Recommendation 4	a. Patients older than 46 years presenting with breast cancer without personal or familial history fulfilling the 'Chompret Criteria' should not be tested for germline *TP53* variants b. Any patient presenting with isolated breast cancer and not fulfilling the 'Chompret Criteria', in whom a disease-causing *TP53* variant has been identified, should be referred to an expert multi-disciplinary team for discussion
Recommendation 5	Children with any cancer from southern and south-eastern Brazilian families should be tested for the p.R337H Brazilian founder germline *TP53* variant

[a]Testing for disease-causing *TP53* variants should be performed before starting treatment in order to avoid in variant carriers, if possible, radiotherapy and genotoxic chemotherapy and to prioritise surgical treatments.

Guidelines for the Li–Fraumeni and heritable *TP53*-related cancer syndromes

Thierry Frebourg[1] · Svetlana Bajalica Lagercrantz[2] · Carla Oliveira[3] · Rita Magenheim[4] · D. Gareth Evans[5] · The European Reference Network GENTURIS

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Genetic consultation

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tp53 gene sequencing: mutation c.993+1g>A

Submitted interpretations and evidence

Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	Supporting information (See all)
Pathogenic (Sep 24, 2020)	criteria provided, single submitter (Invitae Variant Classification Sherloc (09022015)) Method: clinical testing	Li-Fraumeni syndrome Allele origin: germline	Invitae Accession: SCV000754590.3 Submitted: (Jan 07, 2021)	Evidence details Publications PubMed (4) Comment: This sequence change affects a donor splice site in intron 9 of the TP53 gene. It is expected to disrupt RNA splicing and likely results … (more)
Likely pathogenic (Dec 01, 2018)	no assertion criteria provided Method: research	Neoplasm of ovary Allele origin: somatic	German Consortium for Hereditary Breast and Ovarian Cancer Center Cologne,University Hospital Cologne Accession: SCV000924039.1 Submitted: (Feb 22, 2019)	Evidence details
not provided (-)	no assertion provided Method: in vitro	not provided Allele origin: not applicable	MutSpliceDB: a database of splice sites variants effects on splicing,NIH Accession: SCV000925708.2 Submitted: (Nov 07, 2019)	Evidence details

https://www.ncbi.nlm.nih.gov/clinvar/variation/528261/

- DIAGNOSIS: Li Fraumeni Syndrome

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Question 2

What treatment to choose?

- Surgery
- Chemotherapy
- Radiotherapy
- Multimodal treatment

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Exstraskeletal Myxoide Chondrosarcoma

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- Ultra-rare sarcoma (incidence <1/10000000)
- Surgery and neo-adjuvant/adjuvant radiotherapy in localized disease (5-, 10-, and 15-year survival rates of 82–90%, 65–70%, and 58–60%)
- Neo-adjuvant chemotherapy followed by surgery and radiotherapy for metastatic disease (anthracyclines-based/dacarbazine-based/ifosfamide-based regimens)


cancers

MDPI

Review

Extraskeletal Myxoid Chondrosarcoma: State of the Art and Current Research on Biology and Clinical Management

Silvia Stacchiotti [1,*], Giacomo Giulio Baldi [2], Carlo Morosi [3], Alessandro Gronchi [4] and Roberta Maestro [5]

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What treatment in this case?

The case was discussed during a tumor board in the presence of:

- Oncologist
- Radiotherapist
- Pathologist
- Surgeon

The patient was defined inoperable due to the size of the tumor and it was decided to start chemotherapy

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Question 3

Which antineoplastic drug has the greatest genotoxicity?

- Dacarbazine
- Ifosfamide
- Anthracyclines

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Question 3

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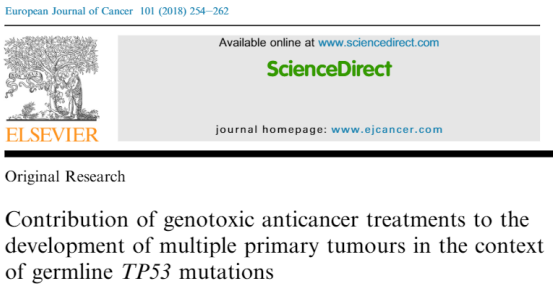
Which antineoplastic drug has the greatest genotoxicity?

- Anthracyclines
- ~~Dacarbazine~~
- ~~Ifosfamide~~


European Journal of Cancer 101 (2018) 254–262

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

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Original Research

Contribution of genotoxic anticancer treatments to the development of multiple primary tumours in the context of germline *TP53* mutations

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Treatment

Chemotherapy: 2 courses of Vincristine/D Actinomycin /Ifosfamide (VAI)

- Vincristine 1,5 mg/m2 Day 1
- D Actinomycin 0,75 mg/m2 Day 1, day 2
- Ifosfamide 3 g/m2 Day 1, day 2

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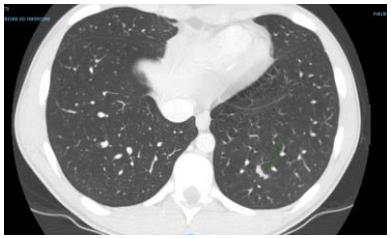
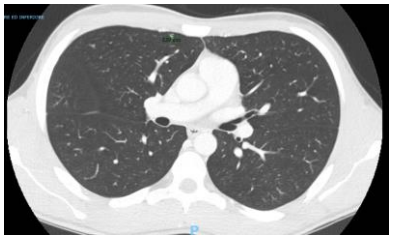
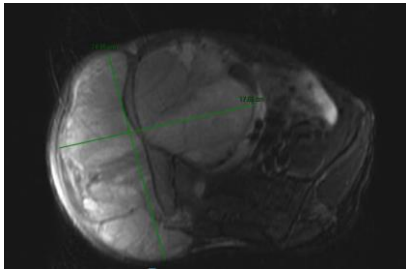
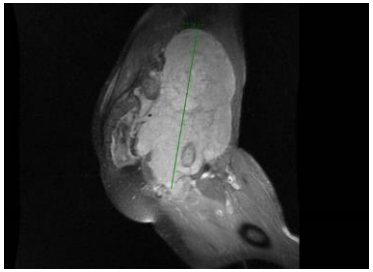
Disease re-assesment

- Total Body CT= appearance of new lung metastasis

- MRI= disease progression (ø 17,5 cm x 19 cm x 23cm; volume increase of 26%)

- Worsening of pain; appearance of inability to walk independently

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Question 4

How to continue the treatment?

- Palliative care
- Anthracyclines regimen
- New drugs-phase 1/phase 2 trials

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New drugs-phase 1/phase 2 trials

- Enrolled into phase 2 trial (E7389-G000-213)
- Eribulin/Irinotecan for the treatment of pediatric patients with relapsed/refractory RMS, NRSTS and EWS

Arms and Interventions Go to

Arm	Intervention/treatment
Experimental: Eribulin mesilate plus irinotecan hydrochloride In Schedules A and B, eribulin mesilate at the dose of 1.4 milligrams per meters squared (mg/m^2) will be administered as an intravenous (IV) infusion on Days 1 and 8 of each 21-day cycle. In Schedule A, irinotecan hydrochloride at the doses of 20 mg/m^2 or 40 mg/m^2 will be administered as an IV infusion on Days 1 to 5 of a 21-day cycle. In Schedule B, irinotecan hydrochloride at the doses of 100 mg/m^2 or 125 mg/m^2 will be administered as an IV infusion on Days 1 and 8 of a 21-day cycle.	Drug: Eribulin mesilate IV infusion Other Name: E7389 Drug: Irinotecan hydrochloride IV infusion Other Name: (S)-4,11-diethyl-39 3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-4-yl-[1,4'-bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate

https://clinicaltrials.gov/ct2/show/study/NCT03245450

- He received 2 courses of chemotherapy

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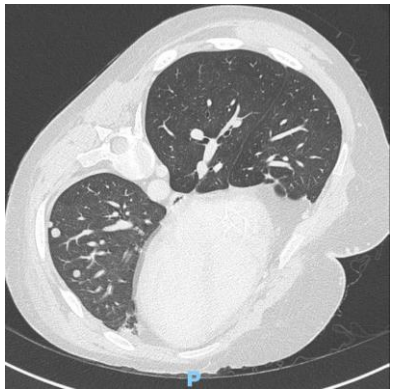
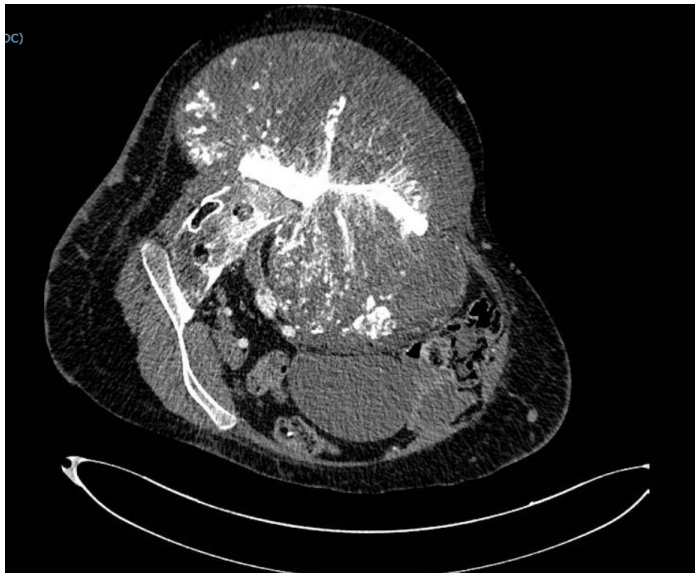
Disease re-assesment

- Total Body CT= dimensional increase of lung metastasis; appearance of abdominal metastases and neoplastic thrombus of the inferior cava vein; progression of the primary mass





- Patient's condition worsened (Karnofsky scale 50%) and pain was not adequately controlled by common painkiller therapy.

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Palliative care

- Caval filter placement to avoid pulmonary embolism
- Pain therapy
- Radiotherapy (low-dose radiation treatment)

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Radiotherapy in palliative care

Low-dose radioterapy in palliative care is helpful to:

- Bone pain improvement
- Nerve compression reduction
- Bowel or urinary obstruction resolution
- Rapid effect on symptoms control

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Discussion point

- How to stage patients with EMC?
- How to decide the best treatment for patient with EMC (tumor board and multidisciplinary discussion)?
- Which drugs to choose in the treatment of EMC and what dosages?
- How the Li-fraumeni syndrome influences the treatment?

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Take home message

- EMC is a rare condition with a specific gene traslocation (NR4A3)
- EMC treatment is based on surgery and radiotherapy for the localized disease
- Metastatic EMC requires multimodal treatment (chemotherapy/radiotherapy/surgery)

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Take home message

- In patients with Li-Fraumeni syndrome, treatment should be tailored on the basis of genotoxic effect of chemotherapy and radiotherapy

- Radiotherapy can be considered for palliative care