DRUG LAB 2: Il Metotrexate e la tossicità neurologica

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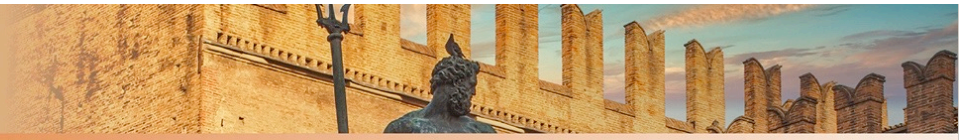
Società Italiana di Radiobiologia



DICHIARAZIONE

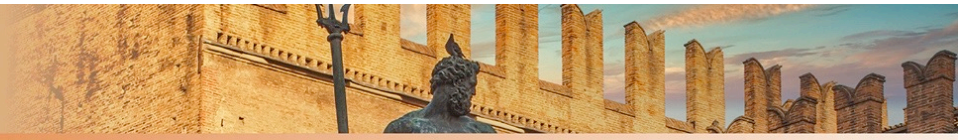
Relatore: Daniela Greto

- ✓ No disclosure to declare

A Radiation Oncologist (me in this case) thinking about Methotrexate…

- ✓Haematological diseases and solid tumors usually not treated w/radiation
- ✓Paediatric tumors indication
- ✓Used in solid tumor more often in metronomic settings

me again…



Therapeutic Indications

Rheumatological and Dermatological Disease:

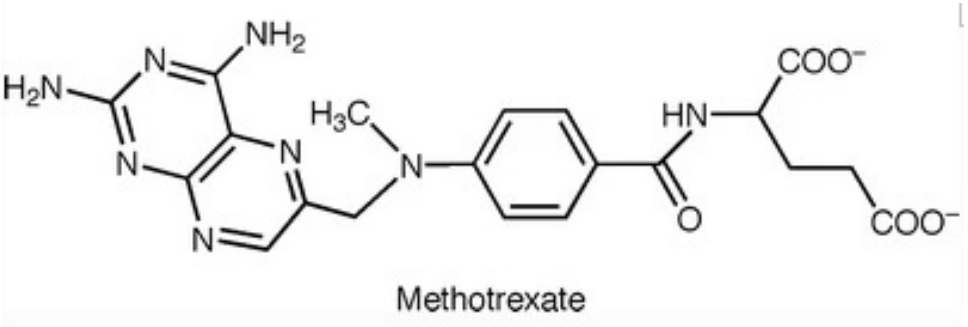
- ✓ Active Rheumatoid Arthritis in adult patients
- ✓ Juvenile Idiopathic Arthritis (JIA) in adolescents and children aged 3 years and over when NSAIDs has been inadequate

Oncology

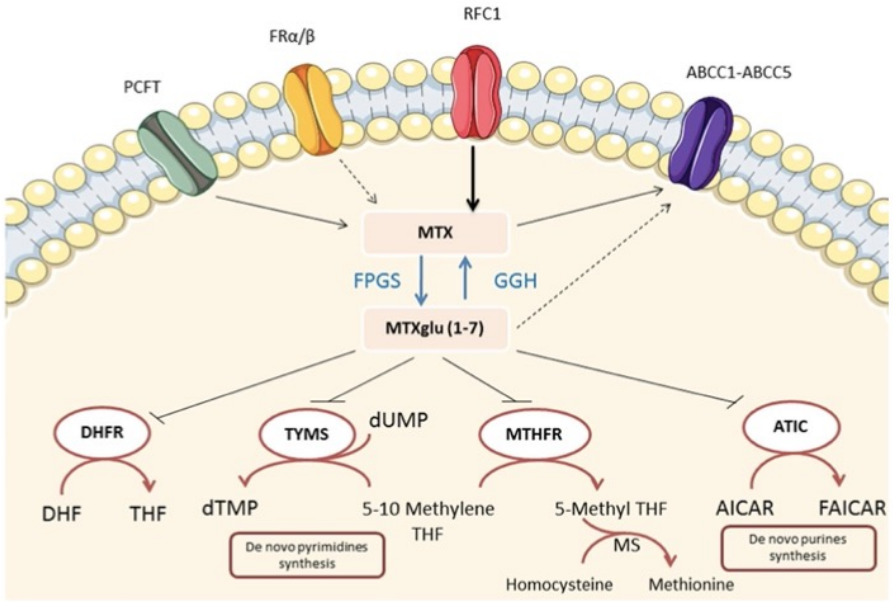
- ✓ Acute Lymphoblastic Leukemia (ALL in adults, adolescents and children aged ≥ 3 years
- ✓ CNS lymphoma
- ✓ Refractory B cell Lymphoma
- ✓ High risk medulloblastoma/PNET
- ✓ High risk Osteosarcoma (< 40 yrs)
- ✓ Solid tumors: lung, breast, uterus, bladder

Pharmacodynamic properties

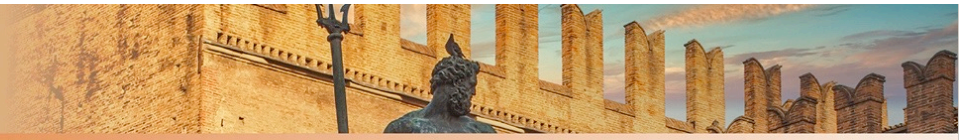
Methotrexate is a folic acid antagonist that, as an antimetabolite, belongs to the class of cytotoxic active substances. It acts by competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis.



Methotrexate



Y. Bedoui, Int. J. Mol. Sci. **2019**, 20, 5023



Pharmacokinetic properties

MTX can be administer via oral, ev, intratecal, intraperitoneal .

The mean bioavailability of methotrexate is approximately 70%, but considerable inter- and intra-individual variations are possible (25-100%). Peak serum concentrations are attained within 1-2 hours.

Distribution

Methotrexate is approximately 50% bound to serum proteins. After distribution, it collects predominantly in the liver, kidneys and spleen in the form of polyglutamates, which can be retained for weeks or months.

The mean terminal half-life is 6-7 hours and demonstrates considerable variations (3-17 hours)

Elimination

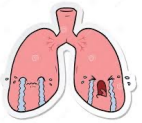
Excretion occurs predominantly in the unchanged form by glomerular filtration and active secretion in the proximal tubule via the kidneys.
Approximately 5-20% of methotrexate and 1-5% of 7-hydroxymethotrexate is eliminated in the bile. There is a pronounced enterohepatic circulation.

Toxicity

Its therapeutic strategy is trial-and-error partly due to an unclear relationship between plasma MTX concentrations and response.

There is high inter-individual variability in Pharmakinetic and Pharmacodynamic for unknown reasons, which leads to unpredictable responses and adverse events .

Common Adverse Reactions (> 1/100 to < 1/10, MeDRA convention):



✓ Blood and Lymphatic System Disorders: Leucocytopenia, Thrombocytopenia, Anaemia

✓ Respiratory, thoracic and mediastinal disorders: Interstitial alveolitis/pneumonia (can be fatal)

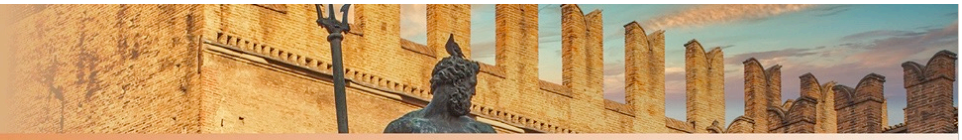
✓ Gastrointestinal disorders: nausea, vomiting, mucositis

✓ Skin: erythema, exanthema, pruritus

Hepatobiliary Toxicity

Temporary increases in transaminases to two or three times the upper limit of normal: frequency of 13-20 %. Persistent elevation of liver enzymes and/or decrease in serum albumin may be indicative for severe hepatotoxicity.

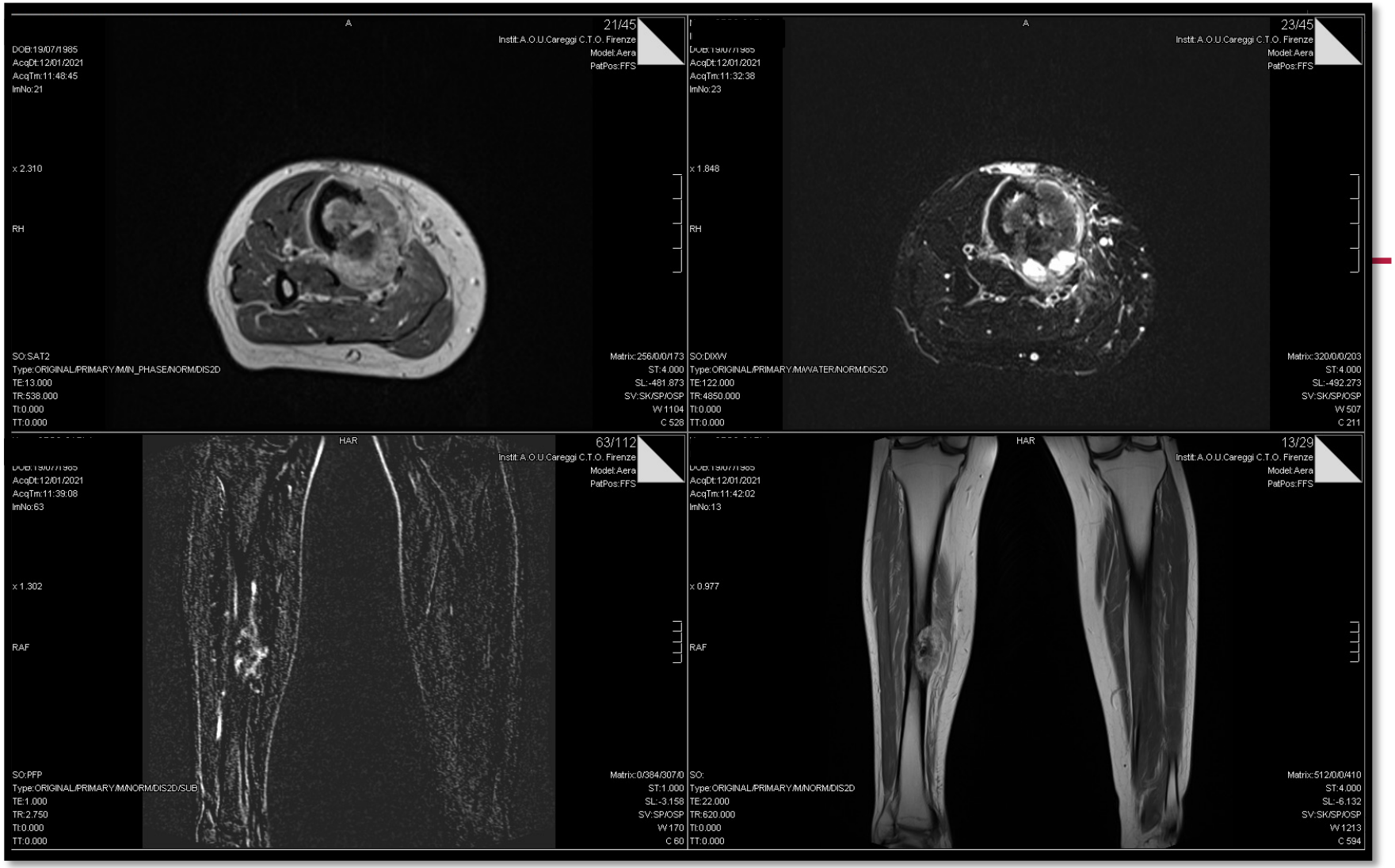
Histological changes, fibrosis and more rarely liver cirrhosis may not be preceded by abnormal liver function tests.
Liver biopsy should be considered on an individual basis taking into account the patient's comorbidities, medical history and the risks related to biopsy.



Clinical Case 1: Hepatobiliary toxicity

Female 32 yo

- ✓ In 2018 thyroidectomy and left cervical lymph adenectomy : multifocal, papillary thyroid carcinoma, 15/51 positive lymph nodes, pT1aN1b. Radiometabolic therapy w/ 1131
- ✓ On November 2020 pain at right leg, Orthopaedic evaluation w/ MRI: osteolytic lesion of 34x23x21 mm localized in the distal right tibial diaphysis , Leg CT confirmed the tibial lesion.
- ✓ Staging TB CT: negative for distant disease
- ✓ Bone Biopsy (12/01/21): osteoblastic Osteosarcoma G3
- ✓ MDT discussion: preoperative chemotherapy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Clinical Case 1: Hepatobiliary toxicity

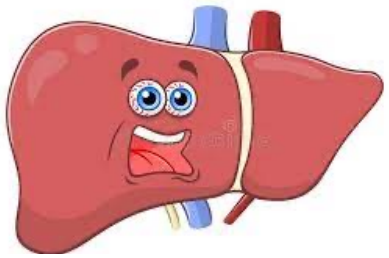
VOLUME 33 · NUMBER 20 · JULY 10 2015
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial

Stefan S. Bielack, Sigbjørn Smeland, Jeremy S. Whelan, Nevyssa Marina, Gordana Jovic, Jane M. Hook.

Methotrexate 12g/m^2

A – Doxorubicin 75 mg/m^2/course
P – Cisplatin 120 mg/m^2/course
M – Methotrexate 12 g/m^2/course
E – Etoposide 500 mg/m^2/course
I – Ifosfamide 14 g/m^2/course
i – Ifosfamide 9 g/m^2/course
Ifn – Interferon α 0.5–1.0 µg/kg weekly

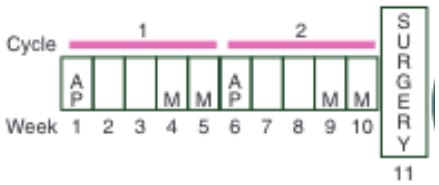


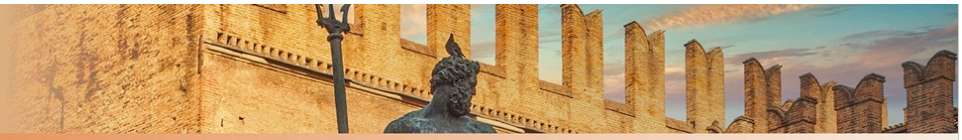
- ✓ **28/01/21 I Cycle: @ 5th weeks**

AST (GOT): 10 → 43 ↑

ALT (GPT): 14 → 716 ↑

Gamma GT: 42 → 383 ↑





Clinical Case 1: Hepatobiliary toxicity

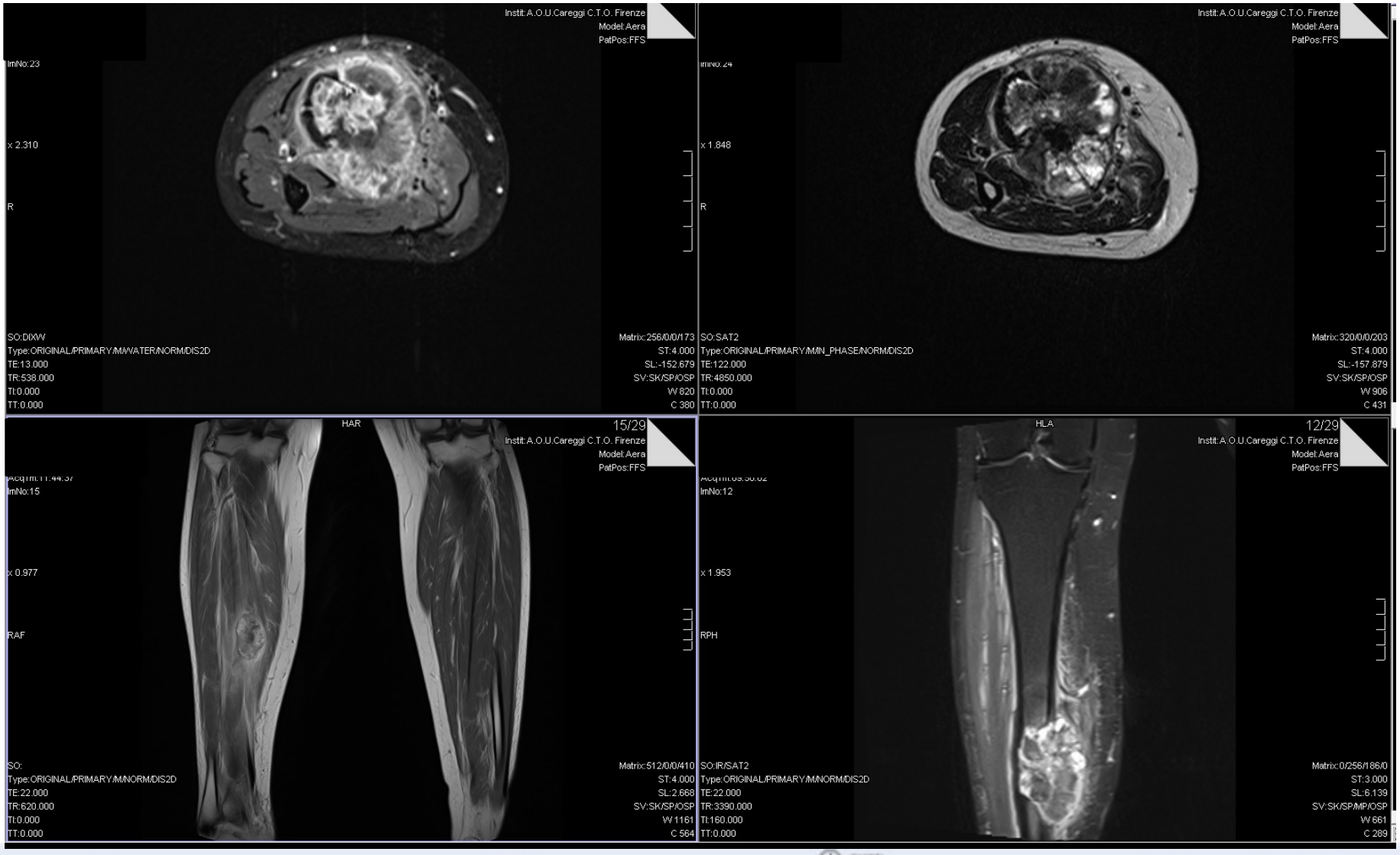
- ✓ G4 liver toxicity, chemotherapy interruption, ev support
- ✓ Elevated level of liver functionality: liver biopsy negative for injuries
- ✓ MDT discussion: surgery time too long due to prothesis building…

Chemotherapy only w/ Adria and CDDP no indication to continue MTX

- ✓ 18/03/21 II Cycle chemotherapy (normalization of liver function)

Restaging

- ✓ TB CT: negative for distant metastasis and MRI
- ✓ MRI gadolinium: increase of the tibial lesion and the extraosseous component (7.7 vs 5.4 cm)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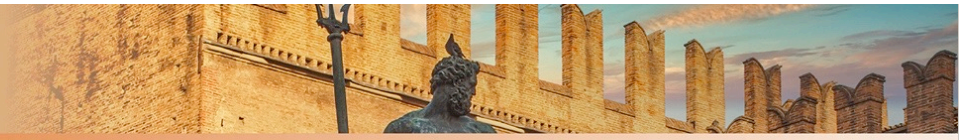


Clinical Case 1: Hepatobiliary toxicity

- ✓16 Apr: surgical tibial resection, grafting of vascular fibula and homologous bone and synthesis with palte and screws
- ✓Histology: High grade Osteosarcoma, Necrosis 78% (Grade II Huvos)
- ✓Postoperative chemotherapy: 4 Doxo + CDDP
- ✓Last follow up 11 Nov 22: negative

Prolonged high serum levels of MTX…such an overdose

The symptoms following overdose predominantly affect the haematopoietic and gastrointestinal systems.

There are reports of deaths from sepsis, septic shock, renal failure and aplastic anaemia.

Glucarpidase (Voraxaze) is the specific antidote for neutralising the adverse toxic effects of methotrexate. A dose of Glucarpidase 50 U/kg should be administered intravenously, and dosing continued until serum level of methotrexate are below 0.005 micromol/L.

- ✓ In the event of a massive overdose, **hydration and alkalinisation of the urine** may be required to prevent precipitation of methotrexate and/or its metabolites in the renal tubules.
- ✓ Effective clearance of methotrexate is reported to be achieved with acute intermittent **haemodialysis** using a high-flux dialyser.

Serum level of Methotrexate (AOUC protocol)

- ✓ Day 0: 19-24:00
- ✓ Day 1: 6,12,18,24:00
- ✓ Day 2: 6,12:00

Every 6 hrs until serum level of MTX < 0.25

…Check urine ph (rv 4.5-7.8)

Clinical Case II: Prolonged high serum levels of MTX

Infant girl, 0 months

- ✓01/12/2015 US during pregnancy (37 wks): brain lesion
- ✓02/12/2015: caesarean section
- ✓Brain MRI w/ gad: 34x20x20 mm lesion of the right caudate nucleus, restriction @ DWI and ADC : high grade glial tumor. Compression of the Monro Foramen determing Hydrocephalus
- ✓04/12/2015 Surgical Biopsy; PNET

Received: 27 January 2020 | Revised: 21 April 2020 | Accepted: 22 April 2020
DOI: 10.1002/pbc.28395

Pediatric Blood & Cancer | SIOP International Society of Pediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

Check for updates

SUPPLEMENT ARTICLE

Brain tumors: Medulloblastoma, ATRT, ependymoma

Sujith Baliga[1,2] | Lorenza Gandola[3] | Beate Timmermann[4] | Horan Gail[5] | Laetitia Padovani[6] | Geert O. Janssens[7] | Torunn I. Yock[1]

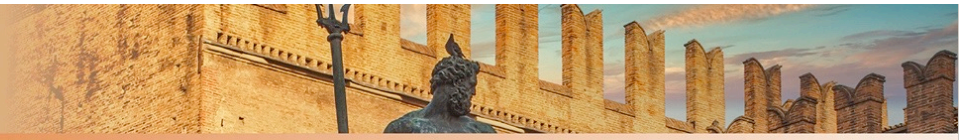
Chemotherapy: AIEOP SNC INFANT protocol

17/12/2015: HD-MTX: 8 g/m^2

@ 12 hrs after injections high level of MTX

↑ Renal function indices
Liver function indices

→ TIN Recovery



Clinical Case II: Prolonged high serum levels of MTX

- ✓ 18/12/2015 EXANGUINOTRANSFUSION
- ✓ 20/12/2015 : Leucocytopenia and ThromboCytopenia
- ✓ Septic Status: Multiresistant Klesbiella Pneumonia
- ✓ Antibiotic Therapy and hemotransfusion
- ✓ Progressive clinical improvement, infection resolution and hematological recovery
- ✓ 31/12/2015: HD-VP16 + GCSF for CPC harvest
- ✓ 201/01/2016: HD EDX+VCR
- ✓ High dose chemotherapy (Thiotepa and Carboplatin)
- ✓ 27/04/2016: @II HD Thiotepa and PBSC reinfusion cardio pulmonary arrest, assisted ventilation, NET
- ✓ Progressive improvement of clinical status, MRI: Partial response and reduction of VL dilatation
- ✓ Follow up: exitus on July 2016

Methotrexate Neurotoxicity

The overall incidence of MTX neurotoxicity ranges from 3 to 10% and varies according to dose, route, and frequency of administration. Factors are high-dose therapy, intrathecal route, young age, and cranial irradiation

Fisher MJ, Am J Neuroradiol. (2005) 26:1686–9

- ✓ MTX markedly induces oxidative stress and reduces antioxidant enzyme levels in the hippocampus. In animal models, MTX-induced degeneration of neurons in the subgranular zone (SGZ) in the dentate gyrus of hippocampus linked to impairment of spatial and recognition memories.
- ✓ MTX treatment causes cell cycle arrest in proliferating cells in the SGZ in the hippocampal dentate gyrus. Therefore, it is believed that exposure to MTX can reduce neurogenesis, and this is closely related to memory deficits.
- ✓ Clinical Syndromes: **Stroke-Like Syndrome and Posterior Reversible Encephalopathy Syndrome**

Welbat JU , Bioch Pharm (2020) 178:114083
Sirichoat A, Neurotoxicology (2022) 92:15-24.

I. Methotrexate-related stroke-like syndrome (SLS)

Neurotoxicity occurring within 21 days of intravenous or intrathecal methotrexate with three characteristics that all need to be fulfilled:

- ✓ New onset of one or more of paresis or paralysis; movement disorder or bilateral weakness; aphasia or dysarthria; altered mental status including consciousness (eg, somnolence, confusion, disorientation, and emotional lability); and/or seizures with at least one of the other symptoms.
- ✓ Either characteristic, but often transient, white matter changes indicating leukoencephalopathy on MRI or a characteristic clinical course with "waxing and waning" symptoms usually leading to complete (sometimes partial) resolution within a week.
- ✓ No other identifiable cause.

Characteristic oval-shaped lesions of the subcortical white matter (mostly frontal or parietal) on MRI are best seen on diffusion weighted (hyperintense) or apparent diffusion coefficient (hypointense) images.
Can be graded 1–5 according to CTCAEv4.03 for encephalopathy.

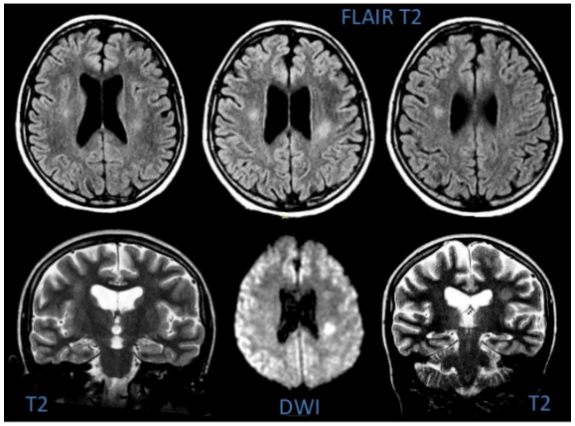
Schmiegelow, Lancet Oncol (2016) 17: e231–39

frontiers | Frontiers in Neurology

ORIGINAL RESEARCH
published: 10 June 2022
doi: 10.3389/fneur.2022.920214

The Clinical Impact of Methotrexate-Induced Stroke-Like Neurotoxicity in Paediatric Departments: An Italian Multi-Centre Case-Series

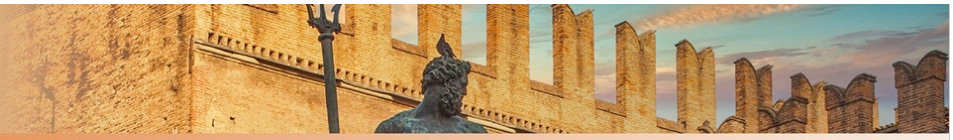
Santangelo,Front Neurol. 2022 Jun 10;13:920214



11 pediatric patients (2011-2021): 11 yrs (range:4-34 yrs)

- ✓ From MTX to SLS : < 3 wks
- ✓ Mean latency symptoms onset: 9.45 days
- ✓ Symptoms: hemiplegia, cranial nerves palsy, paraesthesia, movement/speech disorders, seizures
- ✓ Neuroimaging studies (CT and/or MRI), EEG. Median scoring system: 5 points (maximum 20 points).

Conclusions: linear correlation between the severity of the disease and age in male patients and between age and severity of the disease.



II. Posterior Reversible Encephalopathy Syndrome (PRES)

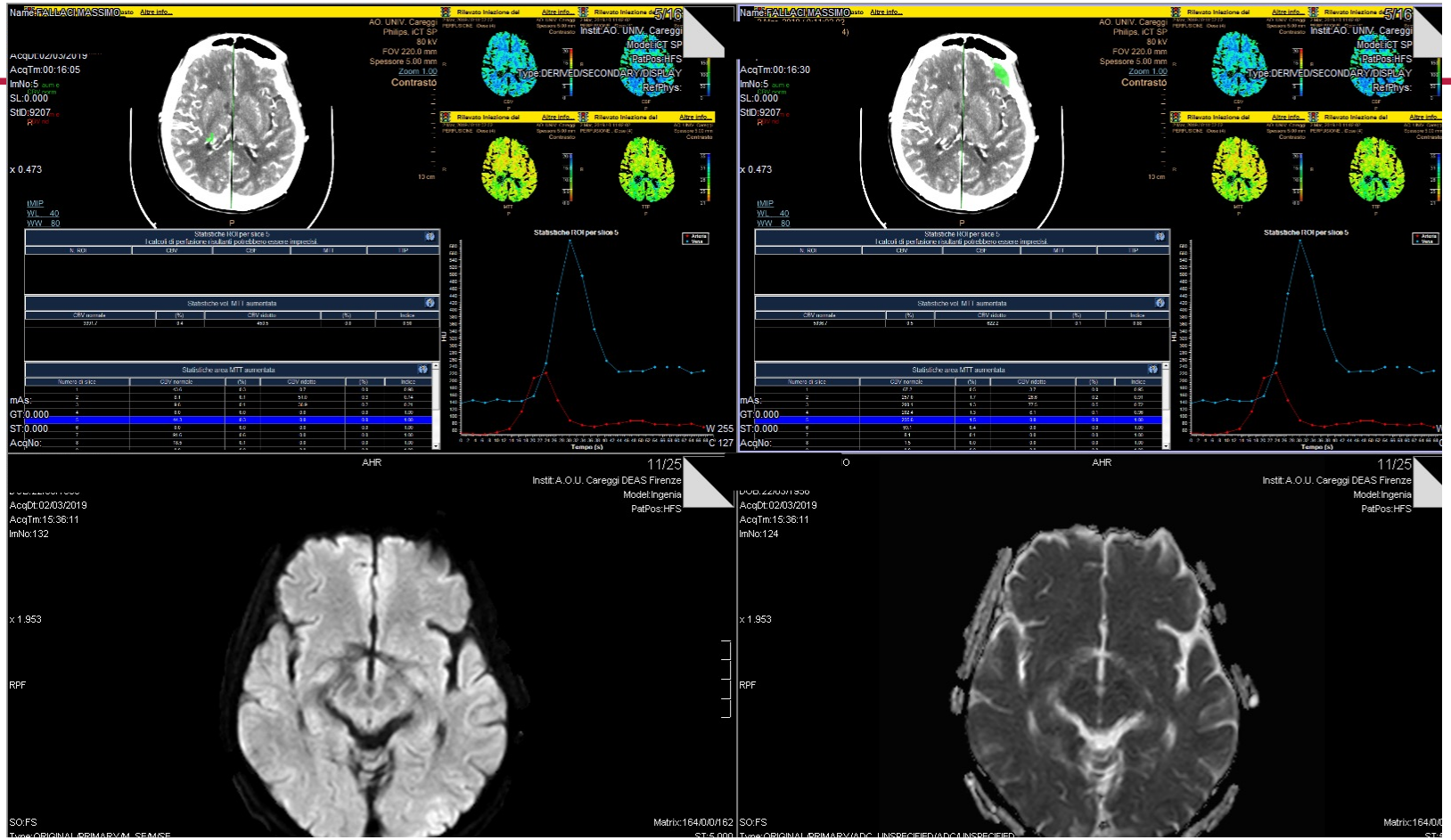
Posterior reversible encephalopathy syndrome is a **clinical** diagnosis based on any combination of transient headache, confusion, seizures, and visual disturbances in combination with characteristic, but transient, contrast-enhanced and diffusion-weighted imaging MRI findings. Diagnosis can be supported by electroencephalogram findings, occurrence during early months of treatment, and presence of arterial hypertension. No grading.

Schmiegelow, Lancet Oncol (2016) 17: e231–39
Dicuonzo, J Child Neu (2009) 24: 1013-1018

PRES: Radiological Findings

The most common conventional magnetic resonance findings are high-intensity areas on T2-weighted imaging, typically located in the periventricular white matter.

These findings are more evident in the acute/subacute neurotoxicity and are associated with white matter damage due to methotrexate, usually termed "leukoencephalopathy."



Courtesy of Dr. Davide Gadda

Clinical Case III: Neurotoxicity

Courtesy of Dr. Iacopo Sardi

Child 4 yrs

- ✓ On Dec 2014 onset of postural instability, headache and vomiting
- ✓ Progressive worsening CT: Hydrocephalus and cerebellar mass

Referred to Meyer's Children Hospital in Florence

- ✓ MRI gad (March 14): 47x40x35 mm cerebellar lesion, nodules on the III ventricle.

Leptomeningeal nodules @ cervical and dorsal spine level

- ✓ DVE and partial removal of disease, histology: Desmoplastic Medulloblastoma, Beta catenin:-, N-MYC amplification :-
- ✓ CSF: negative

VOLUME 27 · NUMBER 4 · FEBRUARY 1 2009

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Hyperfractionated Accelerated Radiotherapy in the Milan Strategy for Metastatic Medulloblastoma

SURGERY

↓

HD-MTX (8 g/m²) → HD-VP16 (2.4 g/m²) → HD-CYCLO (4 g/m²) → CBDCA (800 mg/m²)

↓ 0 ↓ 1 ↓ 4 ↓ 7 weeks

+ G-CSF for CPC harvest

HART 3-4 weeks after CBDCA

If CR pre-HART:
4 weeks after end of RT,
maintenance CT with:
VCR (1.4 mg/m²) every 3 weeks × 18
CCNU (80 mg/m²) every 9 weeks × 6

.... 18 patients

If no CR pre-HART:
4 weeks after end of RT,
thiotepa (900 mg/m²) in 3 days,
for 2 courses
(with a 4- to 6-week interval)

.... 14 patients

CPC: circulating progenitor cells

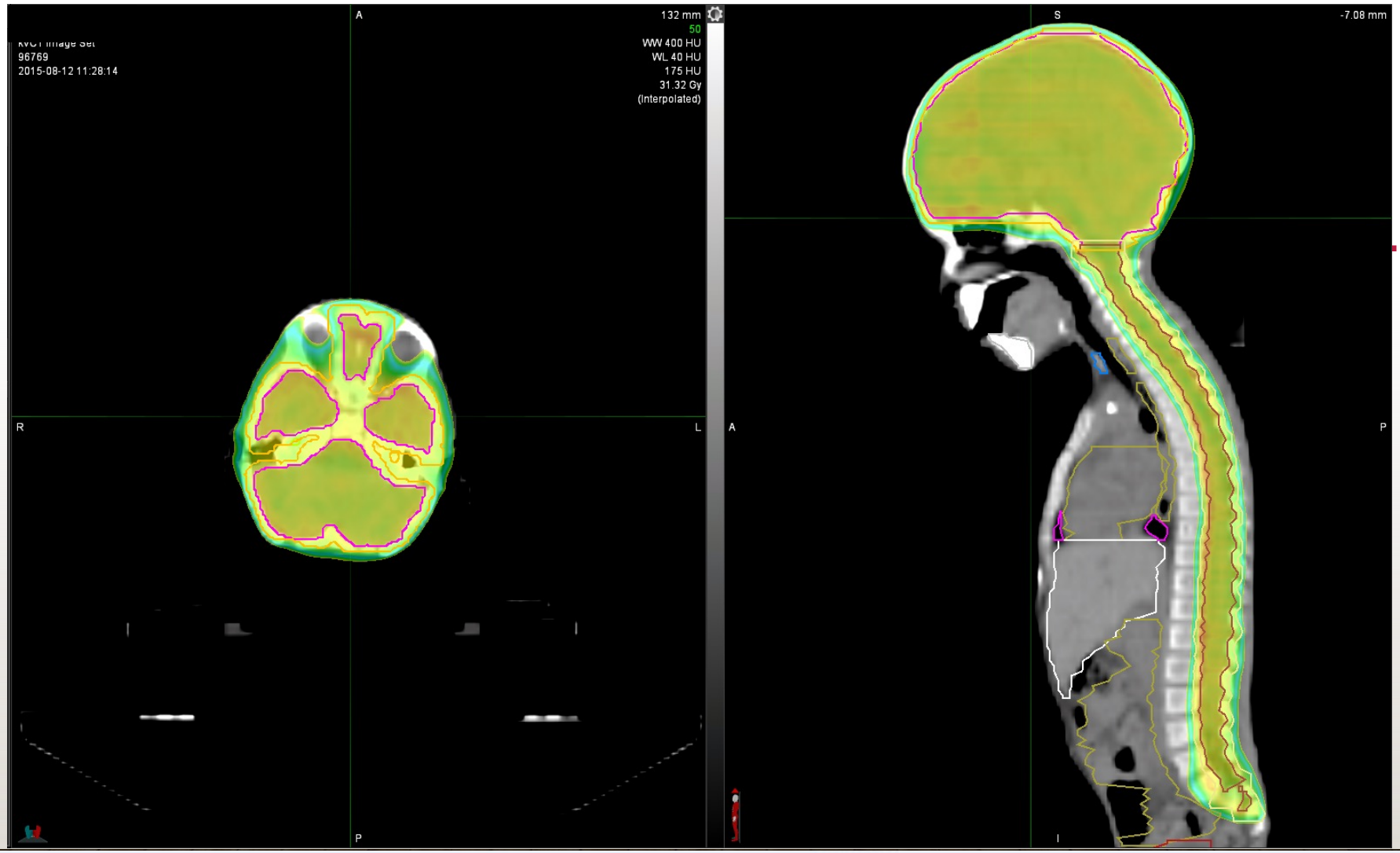
HART doses:
CSI 39 Gy if patients ≥ 10 years...25 patients
CSI 31.2 Gy if patients < 10 years...7 patients

✓ April- July 2015 Chemotherapy

HD MTX: 8 g/m²

✓ MRI w/ gad post treatment: no changes in primary PF disease and metastatic nodules

✓ MDT: CSI sc HART protocol
31.2 Gy: 1.3 Gy BID for 5 days/wk (<10 yrs)
No boost on the surgical bed and residual
No boost on the metastatic sites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96769
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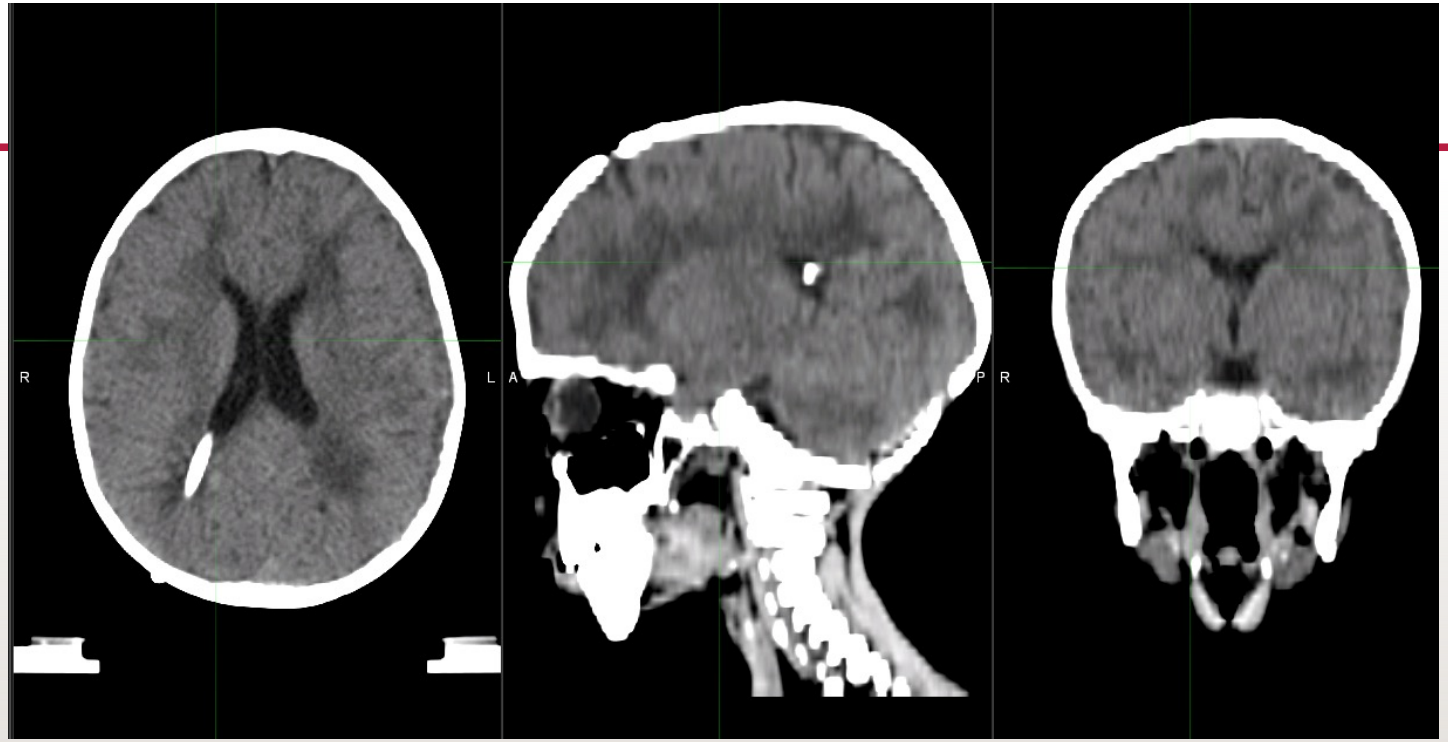
Clinical Case III: Neurotoxicity

- ✓August-Sep HART (anesthesia) : No neurological deficit , Good Tolerance, G2 Hematological Toxicity @ 13 Gy
- ✓After 4 wks: two cycles of Thiotepa and after Maintanance Therapy (VCR and CCNN)
- ✓On Sep 2016: diffuse leptomeningeal enhancement and thickening, resulting in a progressive right crural facial brachial hemiparesis. Stop chemotherapy

Clinical and radiological findings of PRES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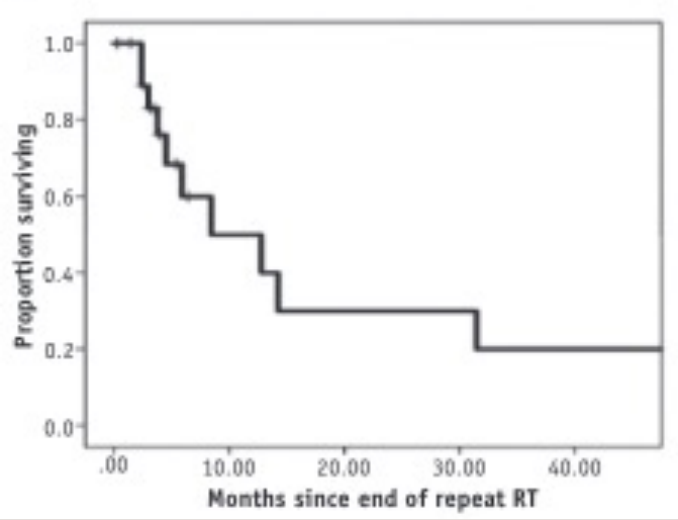
Clinical Case 3 : Neurotoxicity

- ✓On July 2018 pseudonodular lesion of the IV ventricle
- ✓19 July: Suboccipital craniectomy

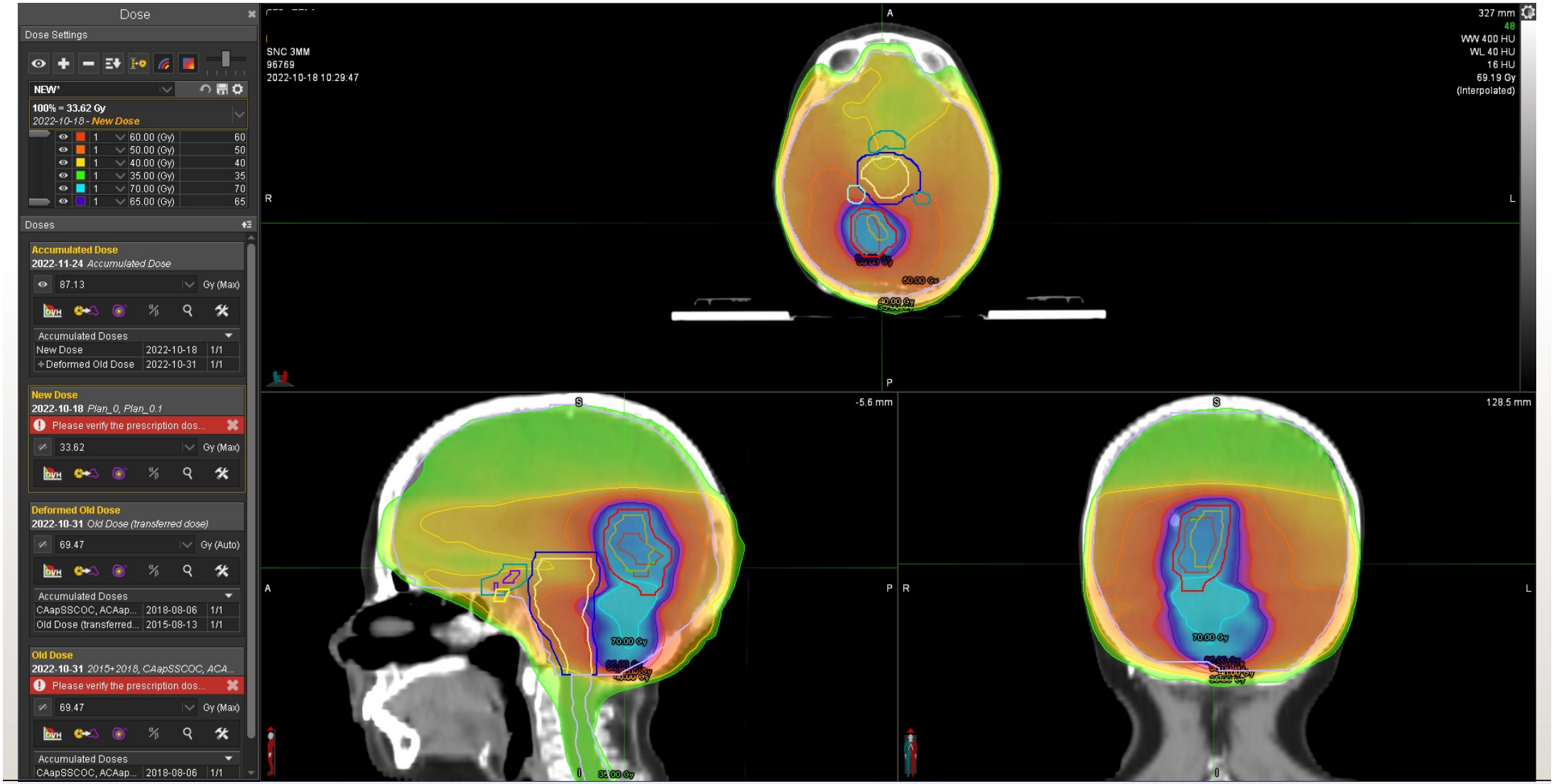
International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

Reirradiation for Recurrent Pediatric Central Nervous System Malignancies: A Multi-institutional Review



- ✓ August 2018: Reirradiation of surgical bed 32.4 Gy in 18 #
- ✓ Stable disease and neurological deficit
- ✓ Started 16 cycles TEMIRI
- ✓ September 2022: Right Temporal Occipital lesion
- ✓ MDT: Surgical excision
- ✓ November 2022: reirradiation of surgical bed



Clinical Case 3 : Caveats

Neurological Deficit:

VOLUME 27 · NUMBER 4 · FEBRUARY 1 2009
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Hyperfractionated Accelerated Radiotherapy in the Milan Strategy for Metastatic Medulloblastoma

Clinical Case 3 : Caveats

Chemotherapy

Radiotherapy

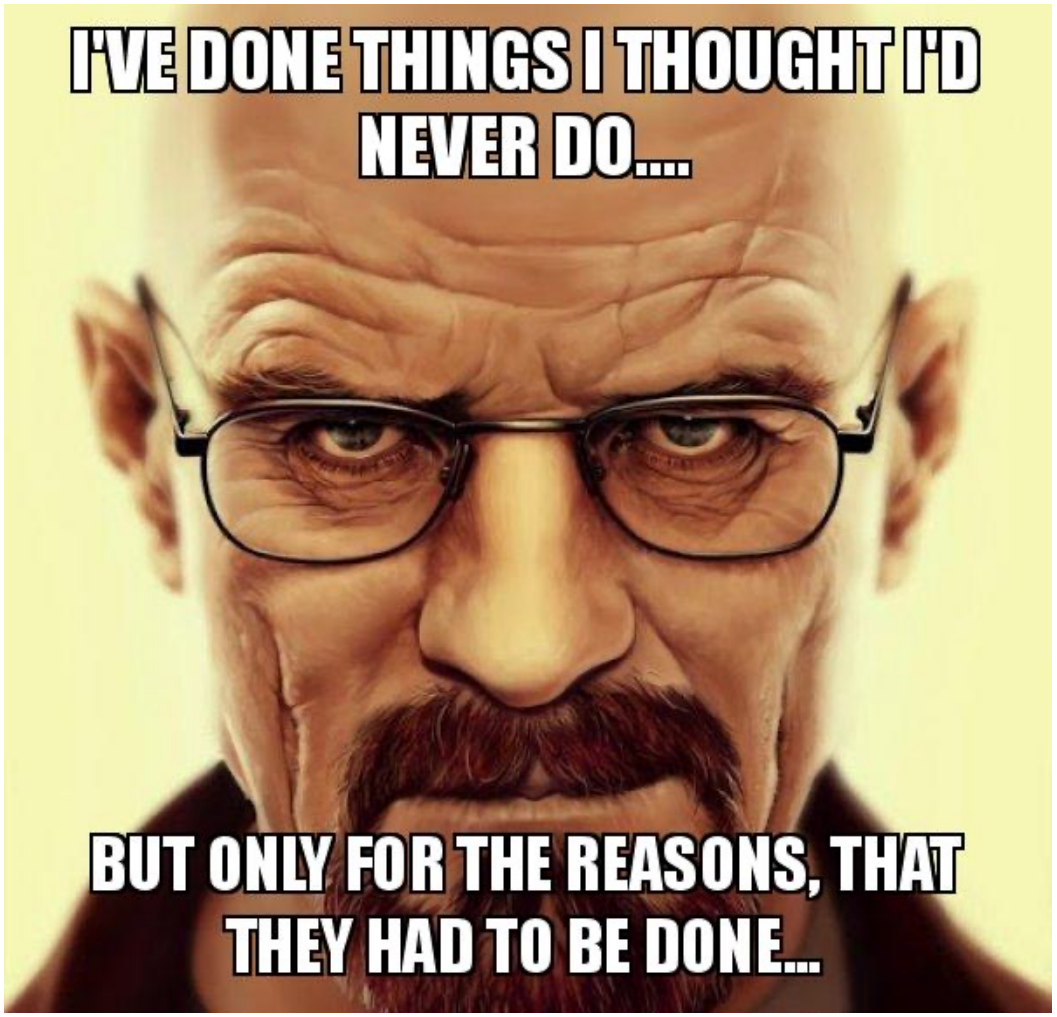
THE TAKE-HOME MESSAGE

- ✓ HD-Methotrexate is a not an easy manageable therapy and needs surveillance protocols
- ✓ MTX associated hepatobiliary toxicity is common in adults and could be fatal

About Neurotoxicity:

Luckly not so common

- ✓ No neurotoxicity data available in the prospective Milan Trial (HD-CT and HART)
- ✓ Only dated experiences on WBRT + HD-MTX in CNS Lymphoma
- ✓ Data reported in fragile patients (Elderly and Paediatrics)


I'VE DONE THINGS I THOUGHT I'D NEVER DO....
BUT ONLY FOR THE REASONS, THAT THEY HAD TO BE DONE...

Thanks !!!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