



**European
Reference
Network**

for rare or low prevalence
complex diseases

Network
Paediatric Cancer
(ERN PaedCan)



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Simultaneous onset of cancer in mother and child: Extremely rare Infantile Choriocarcinoma

Moderation: Teresa de Rojas



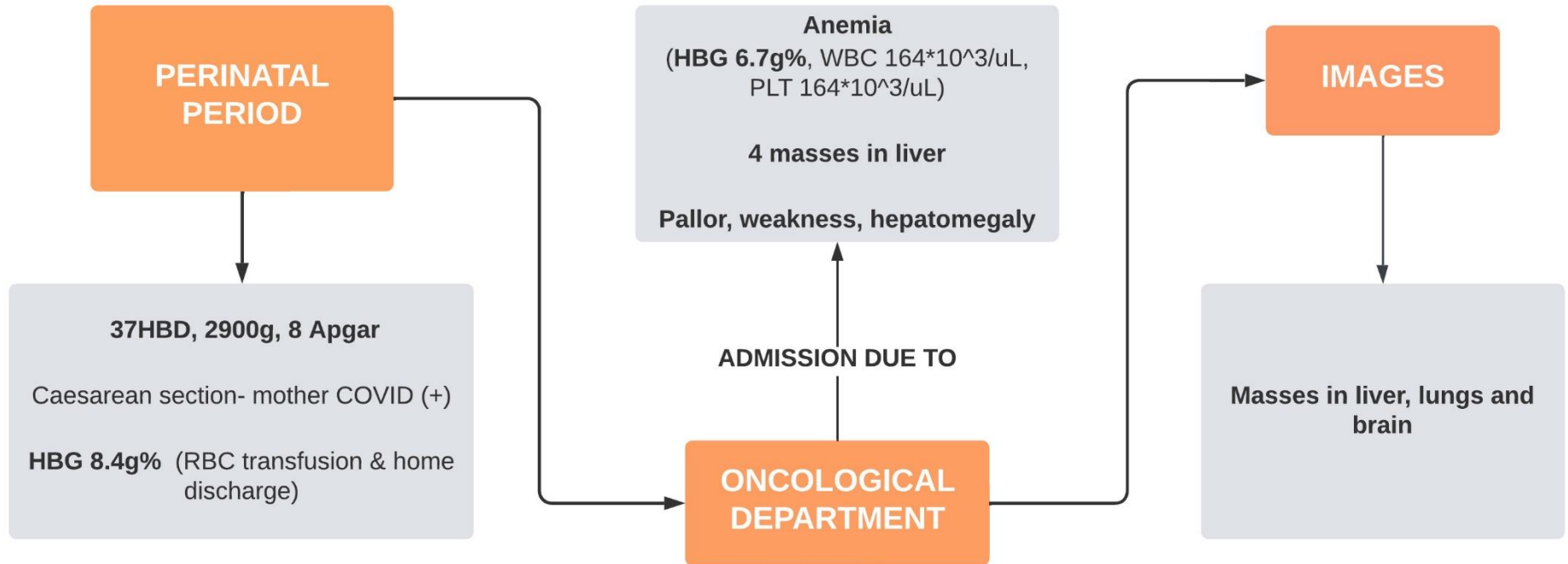
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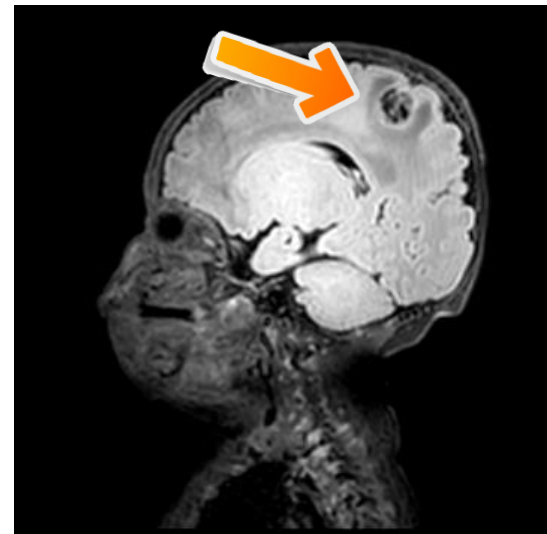
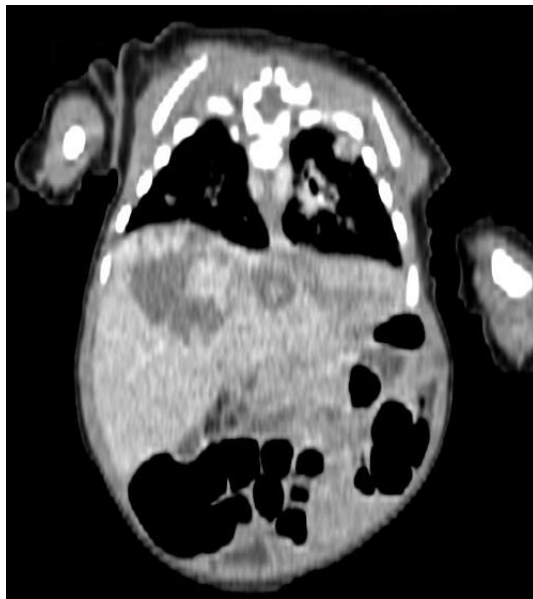
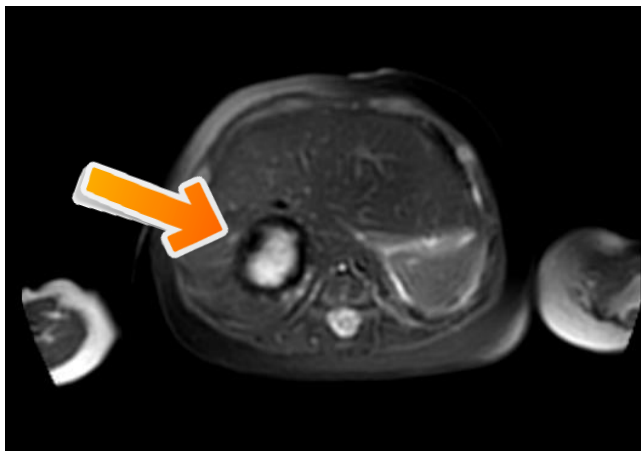
COI declaration

Authors report no actual or potential conflicts of interest.

Case Report



Images



QUESTION 1

What diagnosis would you suspect in a 1-month-old girl with the masses in liver, lungs and brain?

1)
Hepatoblastoma

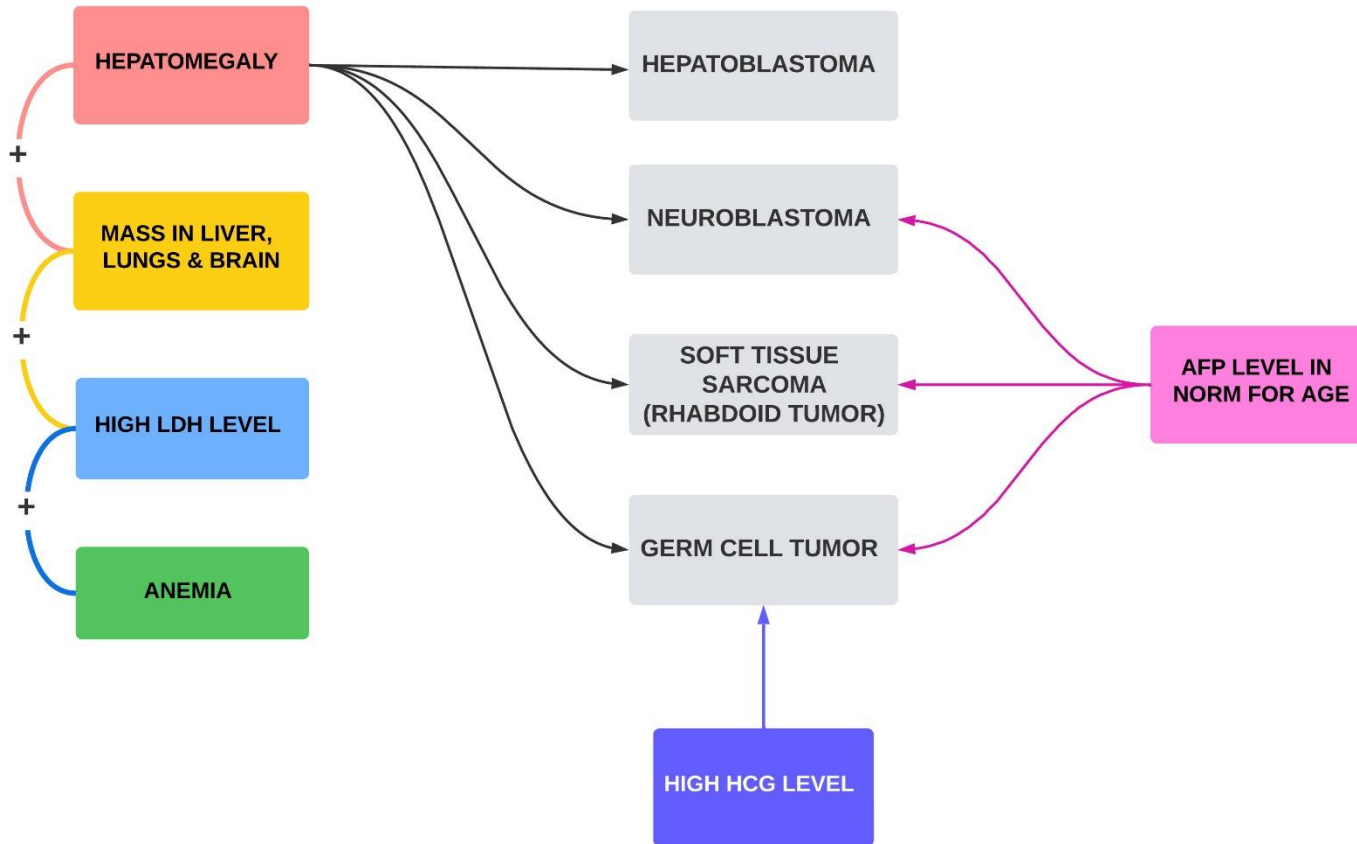
2)
Neuroblastoma

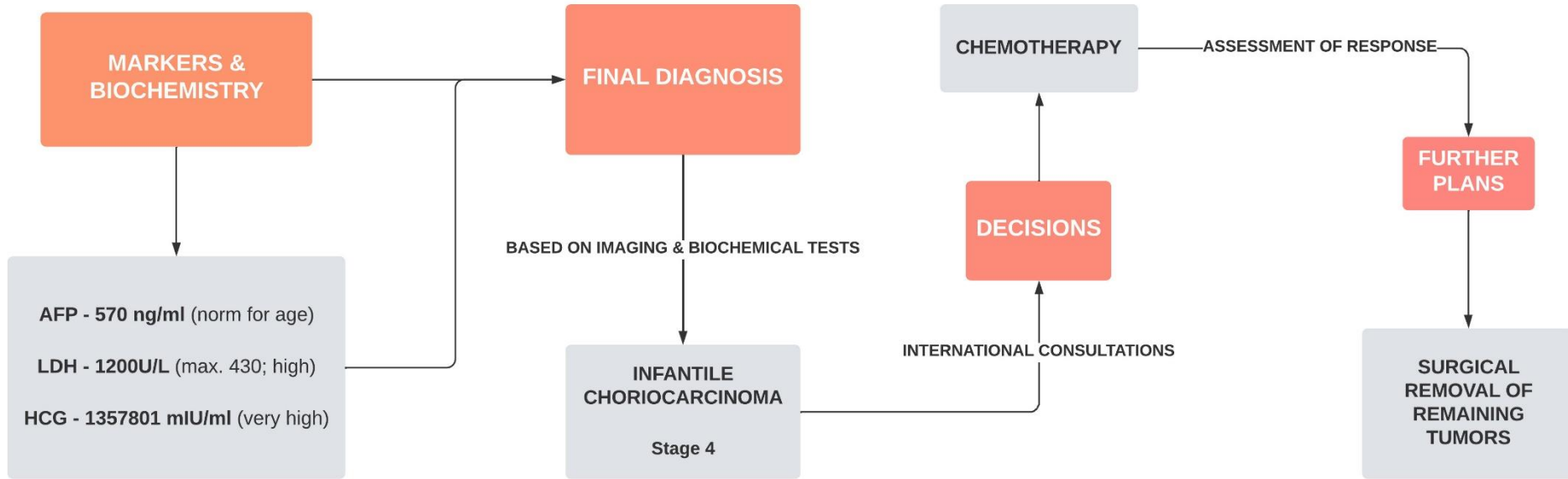
3) Soft Tissue
Sarcoma
(Rhabdoid
Tumor)

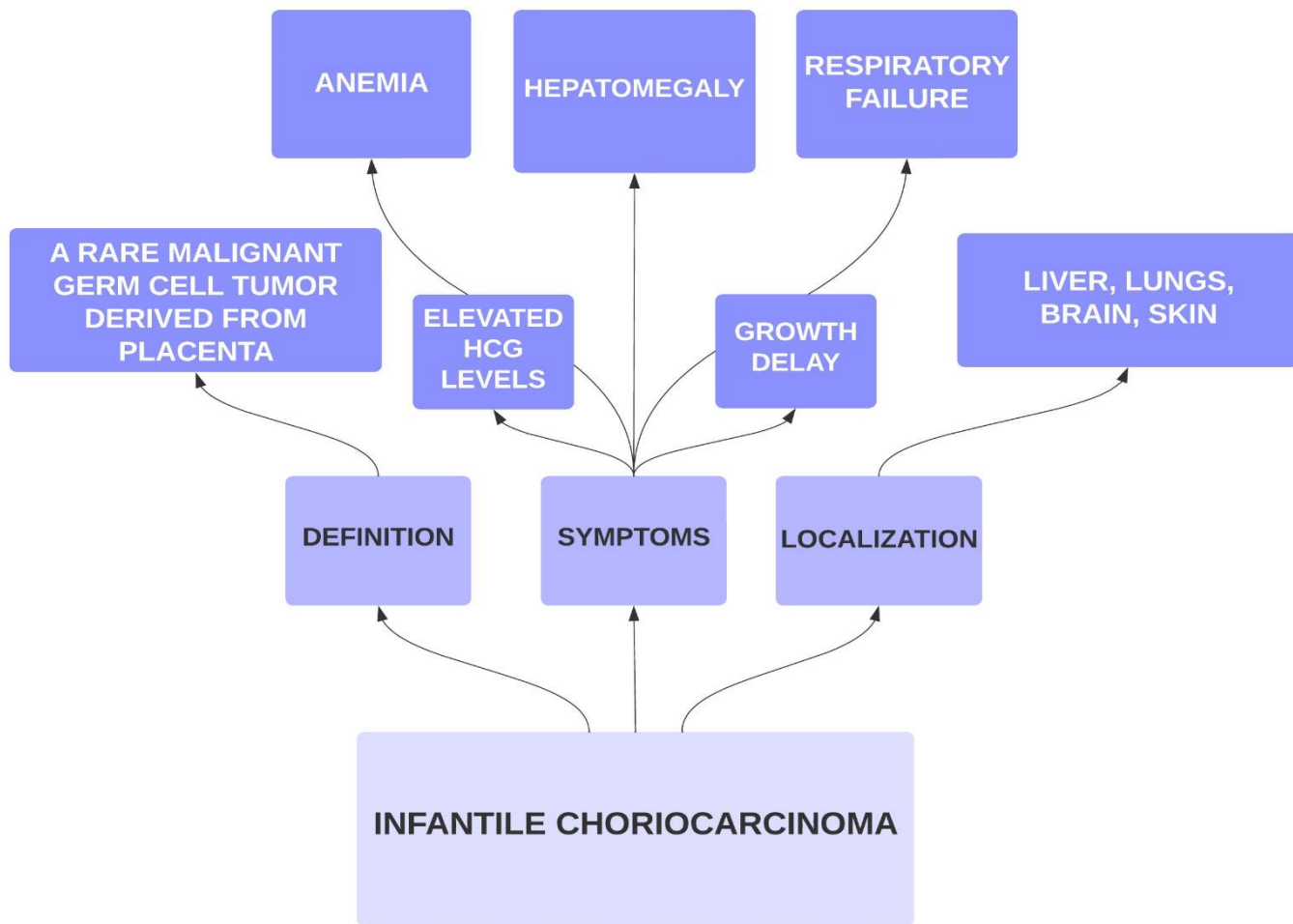
4) Germ Cell
Tumor

5) All above

DIAGNOSIS







QUESTION 2

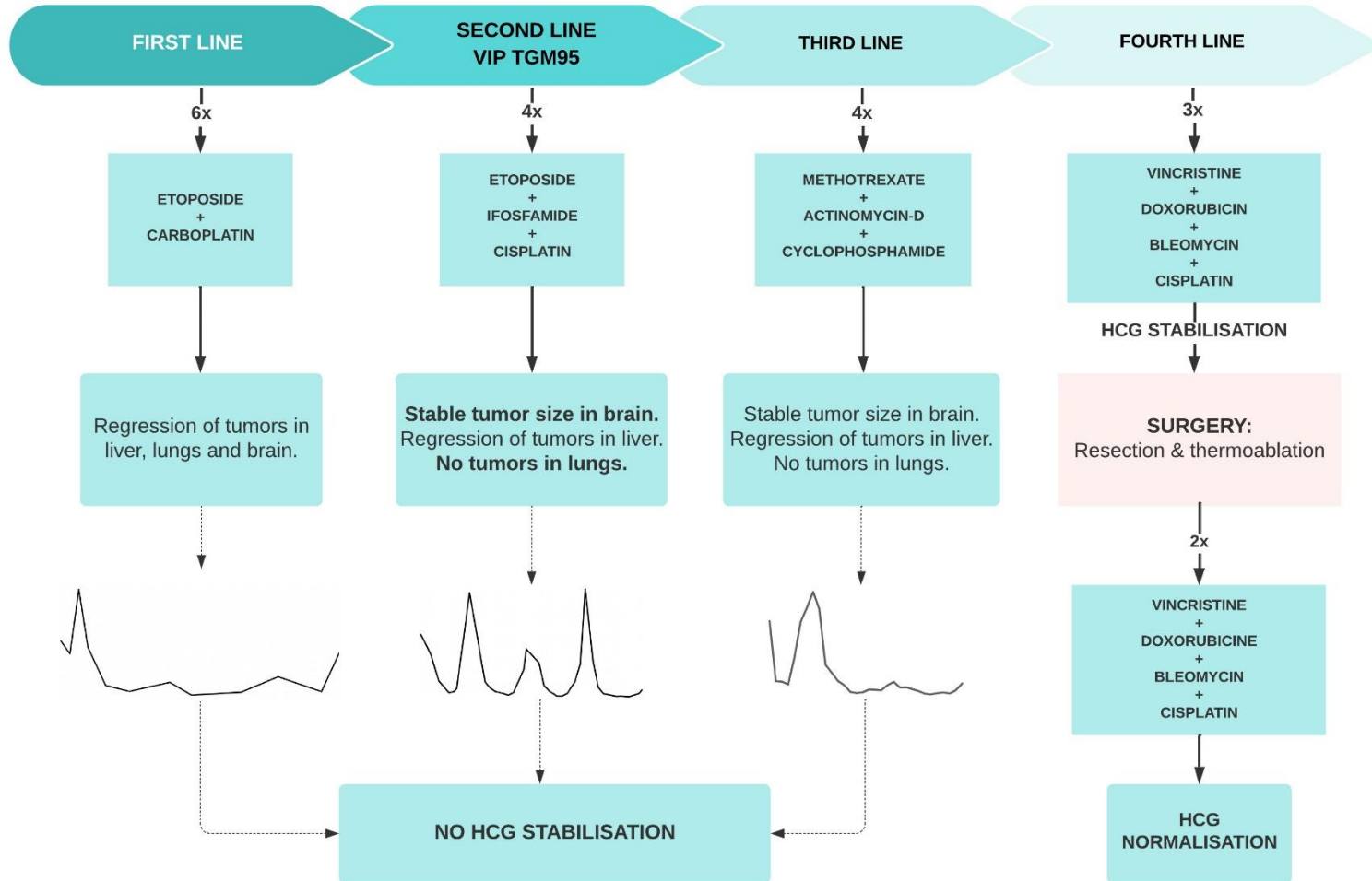
What type of chemotherapy would you suggest for the beginning of the treatment?

1) Methotrexate

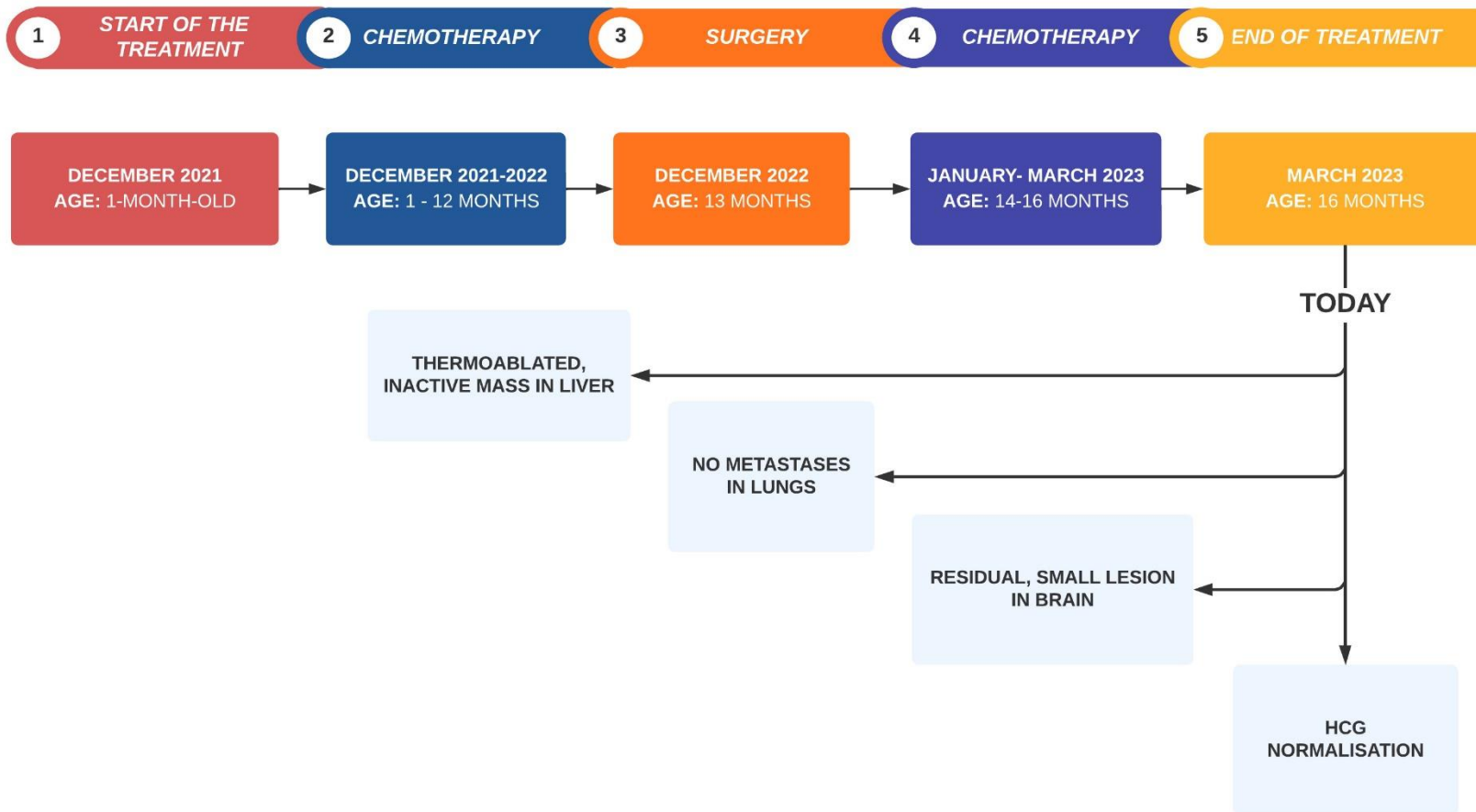
**2) Cisplatin +
etoposide +
bleomycin or
ifosfamide or
methotrexate**

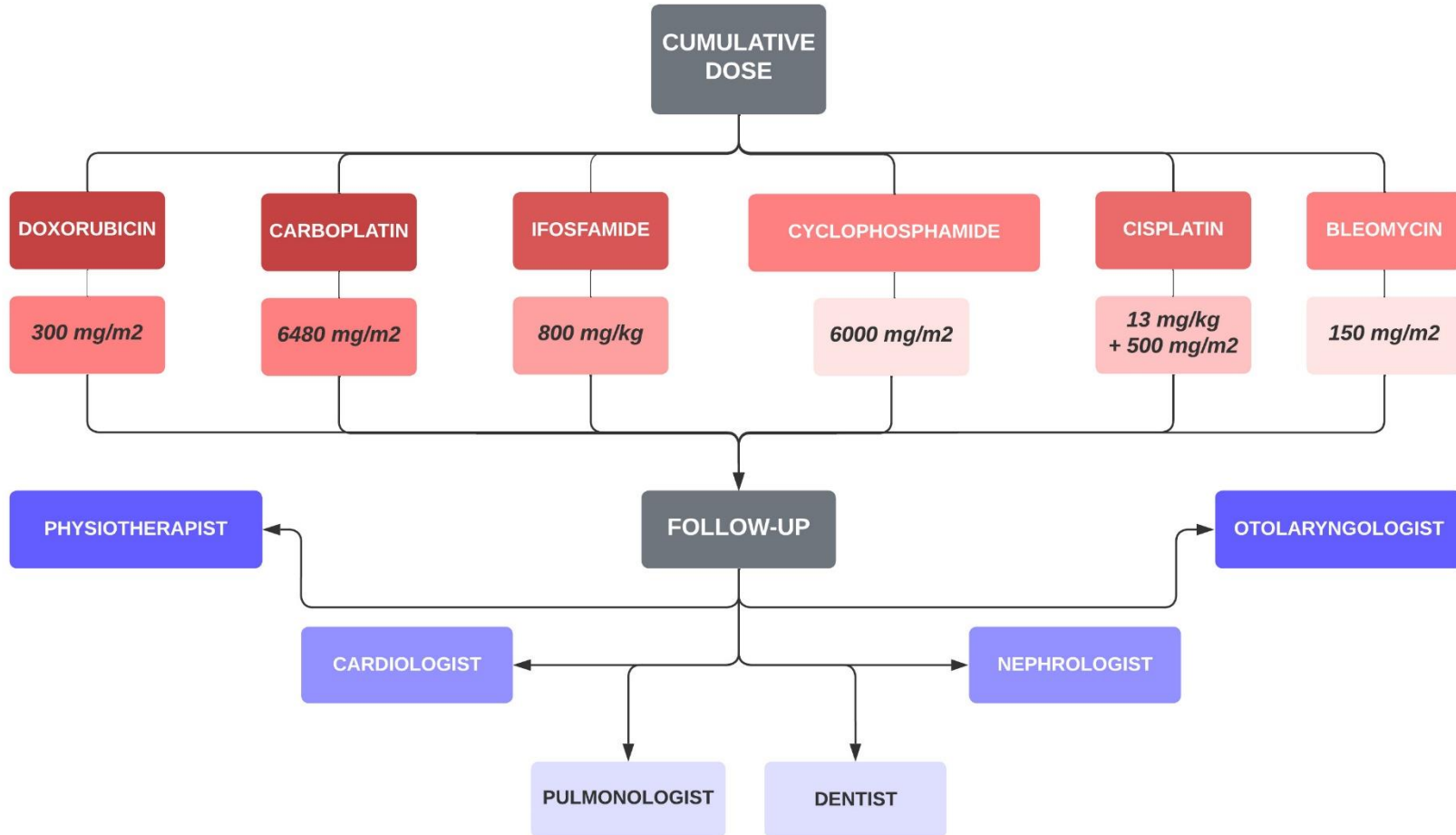
**3) Carboplatin +
etoposide**

4) Other



TREATMENT TIMELINE





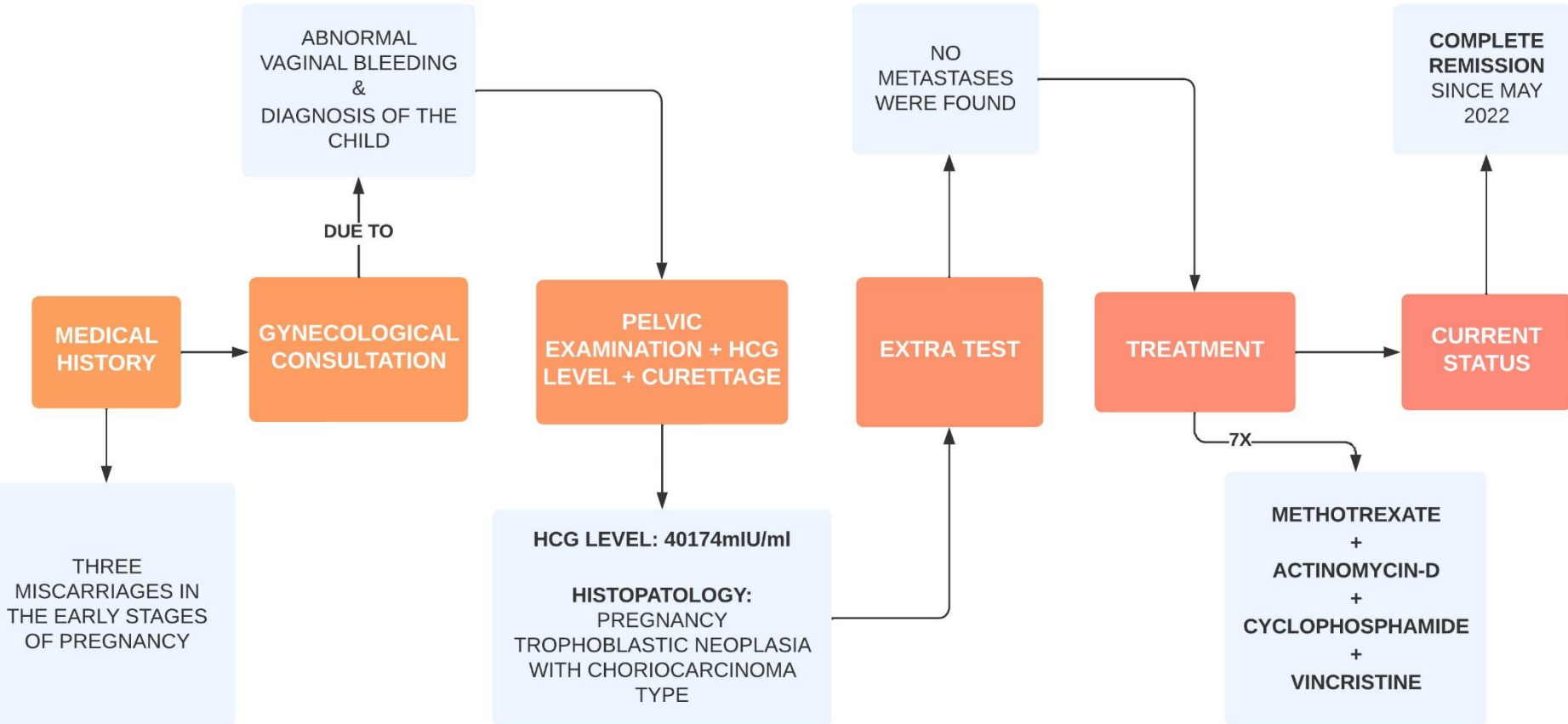
QUESTION 3

What tests should the mother do?

1) None

**2) Pelvic examination &
HCG level (blood)**

MOTHER



DISCUSSION

A - Intraplacental choriocarcinoma

- Literature review: 60 pregnancies
- Mothers:
 - Metastases: 52%; lung, uterus, brain ...
 - Serum HCG: median 228,000 UI/l (100-766 000)
 - Outcome: localized disease, 28/30 alive; metastatic 19 /31 alive
- Children (2 missing data):
 - **20 fetuses: dead**
 - 38 neonates:
 - 20 healthy
 - **16 neonatal complications:** 10 foetomaternal hemorrhage, 4 premature birth, 2 anemia: 1 death
 - 2 with metastases: 1 death; 1 long term CR

B- Transplacental transmission

- **Infectious diseases:**
 - HBV, SARS-CoV-2, HSV-1, CMV, HIV, HPV (?)
 - Trypanosoma Cruzi, plasmodium falciparum,
- **Drugs, tobacco, ...**
- **Malignant diseases:**
 - T / B Leukemia, melanoma
 - Choriocarcinoma
 - Exceptional: small cell lung cancer

C- French recommendations for neonatal choriocarcinoma

- VP 16- Carboplatin if 0-3 months
- VIP – VEB if > 3 months
- Surgery of all remaining lesions

D - Chemotherapy specificities in infants

- Management of chemotherapy in children younger than 1 year of age has to be considered in a developing organism with **maturing organ function** and **physiologic differences** (i.e., body composition or affinity to plasma protein) but also in a pharmacogenetic manner.
- Except targeted therapy, cytotoxic drugs are quite **all administered intravenously (IV)** in childhood, this explain why the absorption is not specifically a problem in infants.
- In case of an oral treatment, different physiologic aspects may interfere with absorption:
 - **Gastrointestinal motility** is low at birth and increase to adult values by 6–8 months old increasing or decreasing the absorption.
 - **Gastric pH is neutral during the first months** and reach the adult values at 2 years old, which modify the bioavailability of drugs

Drugs in infants

- After absorption or IV infusion, drugs diffuse out of vessels and the expansion to tissues in so-called **volume of distribution** (Vd). Vd is partly influenced by body composition:
 - The **proportion of extracellular fluid** volume represent 50% of body weight in preterm newborn, 35% in infants from 4 to 6 months old and 20% in adolescent and adult. Thus, a larger Vd leads to a lower concentration peak.
 - **Fat component** and **blood protein level** interfere also in Vd.
- During infancy the **immaturity of blood-brain** barrier enable a better diffusion of drugs in the central nervous system.

TABLE 10.2 Physiologic Differences in Children That May Influence Drug Disposition

Organ or Compartment	Value at Birth ^a	Age Adult Values Are Reached ^b	Effect on Drug Disposition ^c
Kidney			
Size	↑		
Renal blood flow	↓	1 y	↓ Renal excretion
Glomerular filtration	↓	6 mo–1 y	↓ Renal excretion
Tubular function	↓	1 y	↓ Tubular secretion
Liver			
Size	↑		
Phase I drug-metabolizing enzymes ^d	↓	Variable (oxidative enzymes increase rapidly after birth) ↑ Activity in young children	↓ Metabolic clearance ↑ Metabolic clearance
Phase II drug-metabolizing enzymes ^e	↑ Sulfatation ↓ Other enzymes	Variable (6 mo for glucuronidation)	↓ Metabolic clearance
Biliary excretion	↓	6 mo	↓ Biliary excretion
Gastrointestinal			
Acid secretion	↓	3 mo	Altered drug absorption and stability
Motility	↓	6–8 mo ↑ Transit time in young children	Delayed absorption More rapid absorption

TABLE 10.2 Physiologic Differences in Children That May Influence Drug Disposition

Organ or Compartment	Value at Birth ^a	Age Adult Values Are Reached ^b	Effect on Drug Disposition ^c
<i>Body composition</i>			
Blood volume	↑	Adolescence	
Extracellular fluid	↑	48 mo	↑ Distribution volume
Total body water	↑	4 mo	↑ Distribution volume
Fat	↓	Adolescence ↑ From 4–12 mo of age	↓ Distribution volume of lipophilic drugs ↑ Distribution volume of lipophilic drugs
Cerebrospinal fluid volume	↑	3 y	↑ Distribution volume of intrathecal drugs
Protein binding	↓	1 y	↑ Free-drug levels

^a↓, decreased; ↑, increased (compared with adult values and relative to body surface area or weight).

^bRelative to body surface area or weight.

^cRefer to Table 10.5 to determine which drugs may be affected by alteration of renal, biliary, or metabolic function.

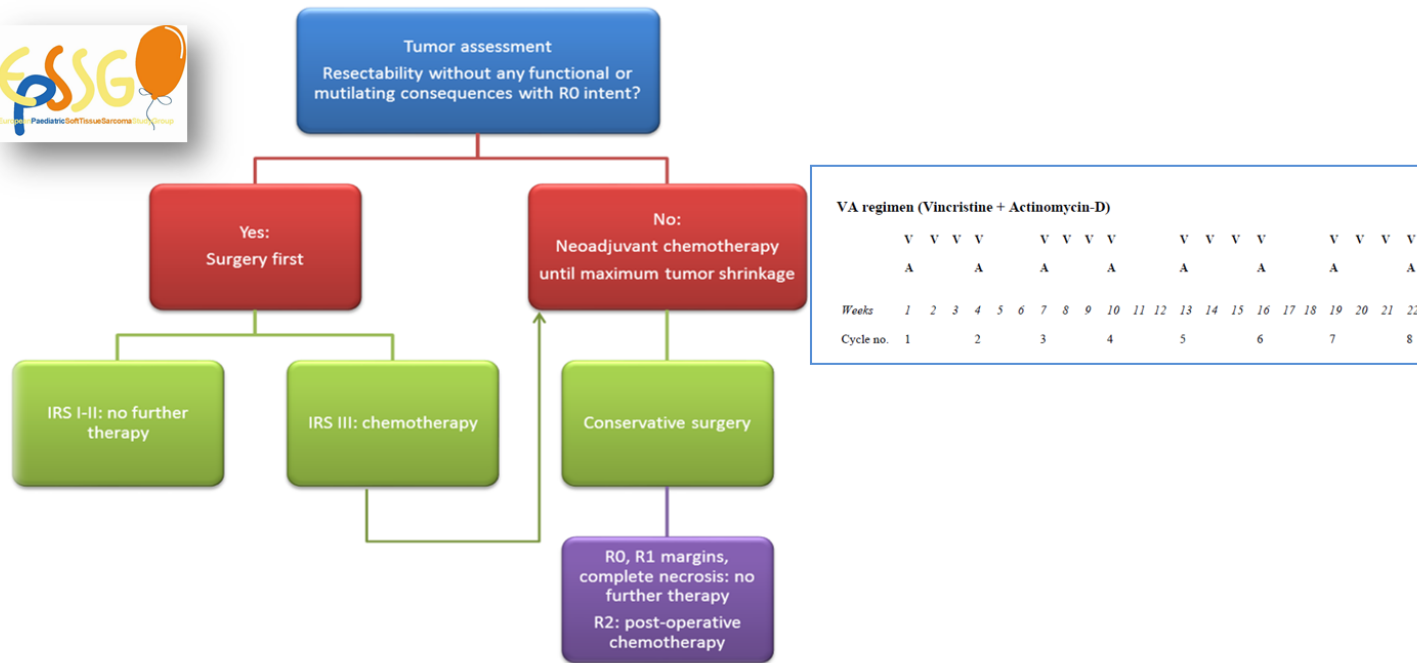
^dOxidation, hydrolysis, reduction, and demethylation.

^eConjugation, acetylation, and methylation.

Daily life prescription

- Limited scientific rationale.
- Heterogeneity exists between tumor types and clinical protocols.
- Weight and age threshold representing the optimal limits for dose reduction are not clearly defined
- Most of the time, **dose reduction** is applied to children **under 1 years of age and/or a weight of 10–12 kg (-30%)** .
- Therefore, in order to avoid unexpected toxicity, an **additional dose reduction** is recommended in some protocols
- To avoid potential specific toxicity in infants, use of some cytotoxic agents is **postponed in younger infants**. In most protocols, anthracyclines are avoided in children age treatments.

EpSSG strategy



Vincristine: Bolus injection, in 10 ml 0.9% NaCl.

- For children < 3 months or < 5 kg: 25 µg/kg/injection for the 2 first cycles (4 injections) then if good tolerance 33 µg/kg/injection for further injections and 50 µg/kg/injection only when age > 6 months and weight > 8 kg;
- For children 3- 6 months and 5-8 kg: 33 µg/kg/injection for the 2 first cycles (4 injections) then if good tolerance 40 µg/kg/injection for further injections and 50 µg/kg/injection only when age > 6 months and weight > 8 kg;
- For children 6-12 months and 8-10 kg: 40 µg/kg/injection for the 2 first cycles (4 injections) then if good tolerance 50 µg/kg/injection for further injections until age > 12 months and weight > 10 kg;

[Orbach 2016]

Protocols	Vincristine	Ifosfamide	D-Actinomycin	Doxorubicin	Etoposide	Carboplatin	Cyclophosphamide	Cisplatin
EpSSG—NRSTS 2005	<p><i>Until 3 months or <5 kg:</i></p> <ul style="list-style-type: none"> – Dose calculated by BW and then reduced to 50%: 0.025 mg/kg/dose – Increased to 0.033 and 0.05 mg/kg/dose at each cycle if well tolerated <p><i>From 3 to 6 months or 6–8 kg:</i></p> <ul style="list-style-type: none"> – Dose calculated by BW and then reduced to 33%: 0.033 mg/kg/dose – Increased to 0.04 and 0.05 mg/kg/dose at each cycle if well tolerated <p><i>From 6 to 12 months or 8–10 kg:</i></p> <ul style="list-style-type: none"> – Dose calculated by BW: 0.05 mg/kg/dose 	<p><i>No IFO until 6 months, substituted by cyclophosphamide</i></p> <p><i>From 6 to 12 months:</i></p> <ul style="list-style-type: none"> – Dose calculated by BW: 100 mg/kg/dose 	<p><i>Until 3 months or <5 kg:</i></p> <ul style="list-style-type: none"> – Dose calculated by BW and then reduced to 50%: 0.025 mg/kg/dose – Increased to 0.033 and 0.05 mg/kg/dose at each cycle if well tolerated <p><i>From 3 to 6 months or 6–8 kg:</i></p> <ul style="list-style-type: none"> – Dose calculated by BW and then reduced to 33%: 0.033 mg/kg/dose – Increased to 0.04 and 0.05 mg/kg/dose at each cycle if well tolerated <p><i>From 6 to 12 months or 8–10 kg:</i></p> <ul style="list-style-type: none"> – Dose calculated by BW: 0.05 mg/kg/dose 	<p><i>No DOXO until 3 months.</i></p> <p><i>From 3 to 6 months or 6–8 kg:</i></p> <ul style="list-style-type: none"> – Dose calculated by BW then reduced to 33%: 0.65 mg/kg/dose – Increased to 0.8 and 1.25 mg/kg/dose <p><i>From 6 to 12 months or 8–10 kg:</i></p> <ul style="list-style-type: none"> – Dose calculated by BW: 1 or 1.25 mg/kg/d (depending of the course) 	<p><i>From birth to 12 months or <10 kg:</i></p> <ul style="list-style-type: none"> – Dose calculated by BW: 3.3 mg/kg/dose 	<p><i>From birth to 12 months or <10 kg:</i></p> <ul style="list-style-type: none"> – Dose calculated by BW: 18 mg/kg/dose – Adapted to renal function and blood dosing (AUC) 	<p><i>From birth to 12 months or <10 kg:</i></p> <ul style="list-style-type: none"> – Dose calculated by BW: 40 mg/kg/dose 	

Table 9.1 Chemotherapy dosing modifications in infants proposed according to age/weight in EpSSG and SIOP protocols

Protocols	Vincristine	Ifosfamide	D-Actinomycin	Doxorubicin	Etoposide	Carboplatin	Cyclophosphamide	Cisplatin
LINES— Neuroblastoma	<i>Weight < 5 kg:</i> – Dose calculated by BW and then reduced to 33%: 0.033 mg/kg/dose <i>Weight 5–10 kg:</i> – Dose calculated by BW: 0.05 mg/kg/dose			<i>Weight < 5 kg:</i> – Dose calculated by BW and then reduced to 33%: 0.67 mg/kg/dose <i>Weight 5–10 kg:</i> – Dose calculated by BW: 1 mg/kg/dose	<i>Weight < 5 kg:</i> – Dose calculated by BW and then reduced to 33%: 3.3 mg/kg/dose <i>Weight 5–10 kg:</i> – Dose calculated by BW: 5 mg/kg/dose	<i>Weight < 5 kg:</i> – Dose calculated by BW and then reduced to 33%: 4.4 mg/kg/dose <i>Weight 5–10 kg:</i> – Dose calculated by BW: 6.6 mg/kg/dose	<i>Weight < 5 kg:</i> – Dose calculated by BW and then reduced to 33%: 3.3 mg/kg/dose <i>Weight 5–10 kg:</i> – Dose calculated by BW: 5 mg/kg/dose	
SIOPEL 4— Hepatoblastoma				<i>Weight < 5 kg:</i> – Dose calculated by BW and then reduced to 33%: 0.67 mg/kg/dose <i>Weight 5–10 kg:</i> – Dose calculated by BW: 1 mg/kg/dose		<i>Carried out according to renal function with target AUC</i>		<i>Weight < 5 kg:</i> – Dose calculated by BW and then reduced to 33%: 1.8 mg/kg/dose <i>Weight 5–10 kg:</i> – Dose calculated by BW: 2.7 mg/kg/dose

BW body weight, *Ifo* ifosfamide, *Doxo* doxorubicin, *EpSSG* European pediatric Soft Tissue Sarcoma Group, *SIOP* International Society of Pediatric Oncology

How to calculate drugs dosages in infants?

- **1 m² = 30 kg**
- So IVA with Ifosfamide 1000 mg/m²/d, day 1 and 2, means 1000/**30**= 33 mg/kg/day days 1 and 2
 - This reduce the dosage for an average of 20%
 - For instance:
 - 7 kg, 0,36 m² = 360 mg/day (in mg/m²) and 231 mg/day (in mg/kg)
- If patient is very young, propose a **further 25-50% dose reduction**

Calculation of right dosage – D-actinomycin

- 1.5 mg = 1500 μ g
- 1500 μ g/m²/30 \rightarrow 50 μ g/kg
- Newborn = 50% of further reduction \rightarrow 25 μ g/kg/injection
- 25 x 3.8 kg = **95 μ g/injection**
- Cosmegen© - Dactinomycin 0.5 mg/vial
 - 1.1 ml of sterile water \rightarrow 500 μ g/ml
 - 95 μ g means **0.19 ml (!)**
 - So new dilution in 4,8 ml of Nacl 0.9% = 5 ml



Conclusions

- Risk of errors: prescription in 0.025 mg/kg or 0.25 mg/kg?
- Risk of over-dosage and under-dosage
- Double verification of all prescriptions

Take home messages

Infantile Choriocarcinoma
is a rare malignant germ
cell tumor that arises from
the
placenta.

In every newborn with
anemia and **liver tumor**,
the serum levels of **hCG**
should
be determined, especially
when the mother has a
positive history of
miscarriage.

In the case of a diagnosis in
a child, the mother should
be consulted by a
gynecologist along with an
assessment of the HCG
level.