SIOP Ependymoma II
An international Clinical Trial for the diagnosis and treatment of children, adolescents and young adults with Ependymoma

Principal Investigator: Dr Didier Frappaz
Study sponsor: Centre Léon Bérard (Lyon)
Coordinating center Belgium: CHR Citadelle Liège
Eligibility criteria

- Ependymoma (WHO grade II and III)
  - Newly diagnosed disease
  - Age less than 22 year old at diagnosis (22-23 years : observational study)
  - Primary tumour location is not spinal cord
  - Not pregnant or nursing
  - Negative pregnancy test
  - Fertile patients must use effective contraception
Study design

• Central review of the pre- and post-operative MRI to confirm the complete resection and to get advice for second look surgery if needed

• Central review of pathology to confirm the diagnosis

• After surgery and central review of radiology and histology, patients will be included in one of the 3 clinical studies, according to
  – The outcome of the first surgical resection (residue or not)
  – Their age and eligibility/susceptibility to receive radiotherapy
  – The localization of the tumour

• Neuropsychological assessment
FIRST STEP
Staging Phase

MRI & Initial diagnosis

Surgery
Post-Operative MRI + CSF

Study entry

Central review of imaging and pathology:
Confirm diagnosis and evaluate need of second look surgery

Patients > 12 months
With no measurable residue
Randomized phase III trial to evaluate the efficacy of post radiation maintenance chemotherapy (VEC CDDP for 15 weeks)

Arm 1

Patients > 12 months
With measurable inoperable residue
Randomized frontline phase II chemotherapy study and exploration of the efficacy of a boost of radiotherapy

Arm 2

Patients < 12 months
and patients not eligible to receive RT
Randomized phase II chemotherapy +/- Valproic acid study

Arm 3

Patients not included in one of the interventional studies
Observational study
REGISTRY
ARM 1
Patients with no measurable residual disease (R0-1-2) WHO Grade II-III ependymoma

No metastasis
Age ≥ 12 months and < 22 years
Adequate bone marrow, liver and renal and liver functions

Randomisation

Conformal RT
GTV (CTV: + 0.5 cm) (PTV: 0.3 cm to 0.5 cm)
59.4 Gy (children < 18 months or with risk factors (*): 54 Gy)
Daily fraction 1.8 Gy, 5 fractions/week.

Observation

Maintenance CT (***)
WEEK 0 => WEEK 5 => WEEK 10 => WEEK 15
- D1: Vincristine (VCR): 1.5 mg/m²
- D1-D3 Etoposide (VP16): 100 mg/m².s.
- D1 cyclophosphamide: 3000 mg/m² in 3 divided infusions.
WEEK 3 => WEEK 8 => WEEK 13
- Cisplatin (CDDP) 80 mg/m².
- Vincristine (VCR): 1.5 mg/m²

(*) multiple surgeries (more than 2) or poor neurological status.
(***) dose adaptation for children less than 10 kg
ARM 2
Patients with measurable inoperable residual disease (R3-R4), WHO Grade II-III ependymoma
No metastasis
Age ≥ 12 months and <22 years
Adequate bone marrow liver and renal and liver functions

Randomisation

VEC-MTX (**)
WEEK 0=>WEEK 3=>WEEK 6
-D1: Vinristine (VCR): 1.5 mg/m²
-D1-D3: Etoposide (VP16): 100 mg/m²
-D1: cyclophosphamide: 3000 mg/m² in 3 divided infusions.
WEEK 2=>WEEK 5=>WEEK 8
-D1: Methotrexate at 8000 mg/m² as a 24 hour IV infusion.

VEC-MTX    VEC

MRI with central Review
2nd look surgery

No residual disease
Residual disease

Conformal RT
GTV (CTV: + 0.5cm) (PTV: + 0.3cm to 0.5cm)
59.4 Gy (children < 18 months or with risk factors( *): 54 Gy)
Daily fraction 1.8 Gy, 5 fractions/week.

Boost of RT of 8 Gy to residue
(Daily fractioned of 4 Gy: 2 fractions)

Maintenance CT (if no prior progression under VEC) (**)
WEEK 0=>WEEK 5=>WEEK 10=>WEEK 15
-D1: Vinristine (VCR): 1.5 mg/m²
-D1-D3: Etoposide (VP16): 100 mg/m²
-D1: cyclophosphamide: 3000 mg/m² in 3 divided infusions.
WEEK 3=>WEEK 8=>WEEK 13
-Cisplatin (CDDP) 80 mg/m²
-Vinristine (VCR): 1.5 mg/m²

( * ) multiple surgeries (more than 2) or poor neurological status.
( ** ) dose adaptation for children less than 10 kg
**ARM 3**

Children<12 months or those not eligible to receive radiotherapy (see national criteria)
Adequate bone marrow liver and renal and liver functions

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**Randomisation**

- **STANDARD CHEMOTHERAPY**
- **STANDARD CHEMOTHERAPY + HDACi = Valproic acid**

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**Maintenance HDACi**
Treatment for one year period
If no progression during frontline chemotherapy

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<table>
<thead>
<tr>
<th>CYCLE N°</th>
<th>CHEMO +/- HDACi**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Vincristine - Carboplatin</td>
<td>D1</td>
</tr>
<tr>
<td>Vincristine - Methotrexate</td>
<td>D15</td>
</tr>
<tr>
<td>Vincristine - Cyclophosphamide</td>
<td>D29</td>
</tr>
<tr>
<td>Cisplatin 2-day Continuous infusion</td>
<td>D43</td>
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<tr>
<td>+/- Valproic acid (*)</td>
<td>Initial dose: 30 mg /kg/day for two weeks in 2 divided doses (BID 15mg/Kg) Increasing weekly up to 40-&gt;50-&gt;60 mg /kg/day in 2 divided doses.</td>
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Number of participants and duration

• Target number of participants - Total: 524

• Target number of participants - Belgium: 40

• Foreseen duration of the study:
  – Inclusion: 5 years
  – Whole study duration: 8 years (5 years inclusion + 1 to 3 year follow-up)

• Participating sites:
  – SUHOPL (CHC Liège-CHR Liège)
  – KUL
  – Ghent
  – HUDERF
  – Ucl
  – UZA Antwerp
  – UZ-Brussel
Panel of reviewers

• Reference Pathology: Pr Michotte - AZ-VUB, Brussels

• Reference Radiology: KUL Gasthuisberg, Leuven

• Reference Neurosurgeon: Dr van Calenbergh, KUL Gasthuisberg, Leuven

• Reference Radiotherapist: Dr Renard, Saint-Luc

• Reference Neuropsychologist: Mme Céline Gryglewicz, CHR Citadelle, Liège
Status of the study

• CTA approval in January 2014

• Submission to the EC under preparation
  – Informed consent translations
  – Intersite contracts
  – Sponsor contract

• Review process
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Thank you for your attention