Childhood Liver Tumours – The SIOPEL experience

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Statistical office: Berne, Switzerland

Strategy Group coordinator office: Gzdank, Poland

WEB System headquarter: Bologna, Italy

* Project leaders’ offices
Childhood Liver Tumours Strategy Group

Trial office: Leicester, UK
International tissue bank: Zurich, Switzerland
Statistical office: Berne, Switzerland
Strategy Group coordinator office: Padua, Italy
WEB System headquarter: Bologna, Italy
Project leaders’ offices
In 2007 there is not a uniformly accepted standard of care for childhood Hepatoblastoma. Thus, different groups give different answers to the same questions.
Status of the arte lecture on Treatment of …Hepatoblastoma

Which is the **standard of care**? … and more precisely

Why, which, when and how much **Chemotherapy**?
Staging of Primary Childhood Liver Tumours

- COG staging system
  - Surgical staging
  - Imaging for metastases
- PRETEXT system (2005 revision)
  - Applicable to all paediatric primary liver tumours
  - Non-surgical staging
  - Imaging is crucial
COG Staging System

- **Stage I:** gross total resection
- **Stage II:** microscopic residual disease (includes tumour rupture and tumour spill at time of surgery)
- **Stage III:** gross residual tumour and/or positive nodes
- **Stage IV:** distant metastases
fissure of the ligamentum teres
PRETEXT

PRETEXT I  left lateral or right posterior section involved
PRETEXT II two adjoining sections free of tumour
PRETEXT III one section free, or two non-adjoining sections free
PRETEXT IV four sections involved
section 1
(caudate)
PRETEXT III
PRETEXT: additional criteria

- C: involvement of segment 1
- E: extrahepatic abdominal disease
- F: multifocal liver tumour
- H: tumour rupture at diagnosis
- M: distant metastases
- N: lymph node metastases
- P: portal vein involvement
- V: involvement of hepatic veins or IVC
**SIOPEL Risk Stratification in Hepatoblastoma**

- **High risk**
  - serum AFP $< 100 \mu g/L$
  - PRETEXT IV
  - E1, E1a, E2, E2a
  - H1
  - M1
  - N1, N2
  - P2, P2a
  - V3, V3a

- **Standard risk**
  - All other patients
Extrahepatic disease
Venous involvement

no involvement

involvement
Venous invasion
Biopsy is usually required

- possible exception
  - age 6 months to 3 years
  - alfa-fetoprotein elevated

SIOPEL recommends tissue diagnosis

Various biopsy methods are available
Hepatoblastoma

Laparoscopic guided liver biopsies
Laparoscopic guided liver biopsies

Hepatoblastoma
Laparoscopic guided liver biopsies

Hepatoblastoma
Laparoscopic guided liver biopsies

Hepatoblastoma
Coaxial biopsy technique
Coaxial biopsy technique
Status of the arte lecture on Treatment of …Hepatoblastoma

Which is the **standard of care**?…and more precisely

Why, which, when and how much **Chemotherapy**?

The European (SIOPEL) point of view
Treatment results in the seventies

Treatment of hepatoblastoma

Treatment results of modern multi-modality treatment strategy !!

SIOP-E1 study
5-years Overall Survival

75% (95 CI 68-82%)

Fig 3. Overall survival with 95% CI.
Which is the standard of care?...and more precisely

Why, when, which, and how much Chemotherapy?

The European (SIOPEL) point of view
Hepatoblastoma

The European way of treating HB - SIOPEL

Pre-operative chemotherapy → Delayed surgery → Post-operative chemotherapy

Chemotherapy before definitive surgery!!
Hepatoblastoma - SIOPEL Experience

SIOPEL TREATMENT STRATEGY

BIOPSY

Pre-operative chemotherapy

DELAYED SURGERY

2 - 3 months

Post-operative chemotherapy

2 months
Status of the art lecture on Treatment of ...hepatoblastoma

Which is the standard of care? ...and more precisely

Why, when, which and how much Chemotherapy?

The European (SIOPEL) point of view
Status of the art lecture on
Treatment of ...hepatoblastoma

Which is the standard of care?...and more precisely

Why, when, which and how much Chemotherapy?

It depends! It depends by....
Standard risk-HB tumour confined to the liver, involving at the most 3 hepatic sectors (PRETEXT I-III),
SIOPEN – Patient stratification concepts

High risk - HB

tumour extending to all 4 sectors (PRETEXT IV) and/or with intra-abdominal and/or distant extrahepatic (M) disease and/or AFP >100 ng/ml
German Pediatric Liver-Tumour Study HB89 - 72 children

**AFP at diagnosis - D. von Schweinitz - Int. J. Cancer 1997**

**Figure 1** - Disease-free survival curves of 4 groups of HB patients with different AFP serum levels; n = 71.
Overall survival of 15 patients with an hepatoblastoma and AFP level < 100 ng/ml – SIOPEL 2 & 3

Thanks, Luarence!
INT-0098
(CCG 8881; POG 8945).
1989 - 1992

16 Undifferentiated small cell (SCUD) HB among 111 completely resected HB

Median age 11 m
Survival rate 9/16
Recurrence rate 63%
Undifferentiated epithelial liver tumors

Small cell undifferentiated hepatoblastoma ( SCUD; and variants )

Undifferentiated hepatoblastoma, intermediate cell type ( ICUD )

Undifferentiated hepatoblastoma, large cell type ( LCUD )

Undifferentiated hepatoblastoma with PNET-like features

Stem cell disorders or offspring of an immature cell lineage ?
Standard risk-HB tumour confined to the liver, involving at the most 3 hepatic sectors (PRETEXT I-III),
CDDP = Cisplatin 80 mg/m²/24 hours i.v. continuous infusion
Doxo = Doxorubicin 60 mg/m²/48 hours i.v. continuous infusion
Hepatoblastoma

The European way of treating HB – SIOPEL

Which chemotherapy?

For standard risk HB – PLADO
(as of to-day)
CDDP = cisplatin 80 mg/m²/24 hours i.v. continuous infusion
PLADO = cisplatin (as above), doxorubicin 60 mg/m²/48 hours i.v. c.i.
SIOPEN 2 pilot study - Treatment results - 5-year survival data by risk category

Overall survival
Progression free survival

SIOPEN 2 pilot study - Treatment results - 5-year survival data by risk category

Overall survival
Progression free survival
SIOPEN 3 Preliminary treatment outcome data

Standard risk HB – All randomized patients

Event Free Survival, standard risk HB

3-year EFS = 80% (95%CI ± 6%)

20 patients had an event
SIOPEN 3 Preliminary treatment outcome data

Standard risk HB – All randomized patients

Overall Survival, standard risk HB

3-year OS = 95% (95%CI ± 5%)

9 patients died, of whom two with HR-HB/ 1 SR-HB died from surgery, 1 from other causes
**CDDP = Cisplatin 80 mg/m²/24 hours i.v. continuous infusion**

**SIOPEL Experience possible standard of care for “our” standard risk HB**

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**Possible standard of care**

- DESLYGDERY
- CDDP CDDP

CDDP = cisplatin 80 mg/m²/6 hours i.v. continuous infusion
STS = 20 gr/m² over 15 minutes infusion, starting 6 hour after the end of CDDP
Sodium thiosulfate (STS)

**Properties**
- $\text{Na}_2\text{S}_2\text{O}_3$
- Water soluble
- Thiol compound
- Reducing agent
- Excreted by kidney
- Biological $T^{1/2}$ 18 min
- Antidote for cyanide

**Relevant Effects**
- Thiol-binding of electrophilic platinum
- Scavenging of reactive oxygen species
- May concentrate in cochlear endo- and perilymph
High risk - HB

tumour extending to all 4 sectors (PRETEXT IV) and/or with intra-abdominal and/or distant extrahepatic (M) disease and/or AFP >100 ng/ml
**CDDP** = Cisplatin 80 mg/m²/24 hours i.v. continuous infusion

**CARBO** = Carboplatin 500 mg/m²  

**Doxorubicin** = 60 mg/m²/48 hours i.v. continuous infusion
SIOPEL 3

Event Free Survival, high risk HB
Overall Survival, high risk HB

SIOPEL 3
Event Free Survival, high risk HB: M0 vs M1

SIOPEL 3

Childhood Liver Tumours
Strategy Group - SIOPEL
SIOPEL 3
Overall Survival, high risk HB: M0 vs M1

% surviving

months

SIOPEL 3
Childhood Liver Tumours Strategy Group - SIOPEL
SIOP EL 1 - HB and metastases

5-year EFS - 31 children

28% (95% CI 12-44%)
Hepatoblastoma
North American Experience

POG 9345
1993 1995
for unresectable or metastatic HB
SIOPENL 4 – High risk HB

Phase II trial

PD

PD

PD or SD

SURGERY incl. OLT

Block B

STOP therapy

unresectable

SURGERY incl. OLT

Block C

Block A1

Block A2

Block A3

D 1

D 29

D 57

D 85
**Cisplatin**
70 mg/m²/day
in 24 hour infusion
on days: 1, 8, 15, 29, 36, 43, 57 and 64

**Doxorubicin**
30 mg/m²/day x 2 days
in 6 hour infusion
to start on days: 8, 36 and 64
Childhood Liver Tumours

Which is the standard of care?...and more precisely

Why, which, when and how much Chemotherapy?

The North American point of view!!
Childhood Liver Tumours

1. Which is the standard of care?...and more precisely

2. Why, when, which and how much Chemotherapy?

   The North American point of view!!
Hepatoblastoma

The American Standard of care - INTEGROUP HEPATOMA STUDY

Primary surgery -> Post-operative chemotherapy -> II look surgery -> Further CT

Chemotherapy after primary surgery
Resect at diagnosis:
PRETEXT I
PRETEXT II
(unifocal tumors with obvious >1cm margin)
Neoadjuvant Chemotherapy to downstage
PRETEXT II (multifocal, < 1cm margin),
PRETEXT III
PRETEXT IV
Still Potentially Unresectable After First 2 cycles of Neoadjuvant Chemotherapy?

PRETEXT III Multifocal  
PRETEXT III +V  
PRETEXT III +P  
PRETEXT IV  

Referral to surgical center with transplant capability, transplant vs. extreme liver resection after 4th cycle of chemotherapy
Childhood Liver Tumours

- Which is the standard of care?…and more precisely

- Why, when, which and how much Chemotherapy?

  The North American point of view!!
Hepatoblastoma

The North American Experience - short historical background

CCG-823F (late ‘80s) - Single arm study - CDDP/DOXO - 66% 3-years OS in unresectable HB

POG trial (late ‘80s) - Single arm study - CDDP/VCR/5-FU - 67% 4-years OS in unresectable HB
Hepatoblastoma

INT-0098 (CCG 8881; POG 8945). 1989 - 1992

CDDP/DOXO (reg. B) Vs CDDP/5-FU/VCR (reg.A)
Hepatoblastoma

INT-0098 (CCG 8881; POG 8945). 1989 - 1992
CDDP/DOXO (reg. B) Vs CDDP/5-FU/VCR (reg.A)
Relevant conclusions

- Treatment outcome was not significantly different between regimen A and regimen B.
- New treatment strategies are needed for the majority of patients with advanced-stage hepatoblastoma.
Grade 3 or 4 toxicities were more common among patients on regimen B than among patients on regimen A. Two toxic deaths were reported for regimen B patients, and both were attributable to continuous infusion DOX-induced cardiomyopathy. No toxic deaths were observed for regimen A.

CDDP/VCR/5-FU the Gold Standard
Hepatoblastoma - North American Exp.

The North American Experience - Late ‘90s

CDDP/VCR-5-FU Vs CDDP/CARBO

Study prematurely closed for excess of failures in the CDDP/CARBO arm
Hepatoblastoma - North American Exp.

POG 9345
1993 1995
for unresectable or metastatic HB
INT-0098 (CCG 8881; POG 8945). 1989 - 1992

HB Completely resected; purely fetal histology pattern with low mitotix index (< 2 per 10 higher power field)
Hepatoblastoma - North American Experience

INT-0098 (CCG 8881; POG 8945). 1989 - 1992

Relevant conclusions

All nine patients with stage I-FH disease treated with low-dose bolus IV DOXO were alive and free of disease at the time of last contact –

Pure Fetal HB completely resected represent a FH HB and actually may be cured with surgery alone
Which is the standard of care?...and more precisely

Why, when, which and how much Chemotherapy?

It depends! It depends by their three risk categories!
COG Hepatoblastoma Treatment Strategy

- **Low Risk= Diminish Toxicity**
  - resection at diagnosis, PRETEXT 1 and PRETEXT 2 with >1 cm radiographic margin
  - Stage I, pure fetal histology, Surgical resection alone
  - Stage I, 2 cycles adjuvant chemotherapy

- **Intermediate Risk= Increase Survival**
  - C5V vs. C5V-D
    - Four cycles neoadjuvant
    - Two cycles adjuvant
  - Stage III Resection PRETEXT 2 <1cm PRETEXT 3
  - Transplant Referral PRETEXT 3 multifocal, V,P or PRETEXT 4, PLUTO registry all transplants

- **High Risk=Identify New Agents**
  - Stage IV
  - Small Cell Undifferentiated
  - AFP < 100 at diagnosis
  - Irinotecan/Vincristine up-front window chemotherapy
COG Hepatoblastoma Treatment Strategy

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The Gold standard - PRETEXT I and II

The present

COG
S + 4 cycles “C5V”
“pure fetal” nothing!

SIOPEL
4 PLADO + S + 2 PLADO

The future

COG
S + 2 cycles “C5V”
“pure fetal” nothing!

SIOPEL
4 CDDP + S + 2 CDDP

C5V = Cisplatin, Vincristine, 5-Fluorouracile
S = surgery
The Gold standard - PRETEXT III

**The present**

COG
4 “C5V”-S- 2 cycles “C5V”

SIOPEL
4 PLADO-S-2 PLADO

**The future**

COG
“C5V” Vs “C5v”- Doxo

SIOPEL
4 CDDP-S-2 CDDP

C5V = Cisplatin, Vincristine, 5-Fluorouracile
S = surgery
The Gold standard - PRETEXT IV

The present

COG
4 “C5V”-S- 2 cycles “C5V” & transplant

SIOPEL
CARBO/DOXO/CDDP -S- & transplant

C5V = Cisplatin, Vincristine, 5-Fluorouracile
S = surgery

The future

COG
“C5V” Vs “C5v”- Doxo & transplant

SIOPEL
Intensified CDDP-S- & transplant
The Gold standard – M+ Hepatoblastoma

The present

COG
4 “C5V”-S- 4/2 cycles “C5V”

SIOP/EL
CARBO/DOXO/CDDP -S- …

C5V = Cisplatin, Vincristine, 5-Fluorouracile
S = surgery

The future

COG
Experimental “window approach” Ironotecan/V

SIOP/EL
Intensified CDDP-S-
The early endoderm – liver pathway
Maturity is achieved several months after birth resulting in a prolonged formative period with an increase vulnerability to developmental aberration and neoplasia.

Cerebellum the main site of post-natal cell proliferation within the CNS.
**WNT and SHH signalling pathways**: regulators of wide range of developmental events particularly in the cerebellar granule cells

PTCH binding normally activates a signalling pathways that has a pleiotropic roles in development

SHH signalling regulates granule-cell proliferation during normal cerebellum development...SHH expressed by the Purkinje cells

Nature Review, Cancer June 2005
Molecular regulation of granule cell proliferation

Purkinje cells are established quite early in cerebellum development.

Mutation of the PTHC gene results in a constitutive activation of this pathway, leading to increase proliferation of the granule-cell precursors.

Purkinje cells are established quite early in cerebellum development.
Medulloblastoma treatment – future prospectives
On behalf of the International Childhood Liver Tumour Strategy Group - SIOPEL
Hepatoblastoma – The SIOPEL experience

Childhood Liver Tumours Strategy Group - SIOPEL