Anti-tumor efficacy in SIOPEL 6 - a multi-centre open label randomised phase III trial of the efficacy of sodium thiosulphate (STS) in reducing ototoxicity in patients receiving cisplatin (Cis) monotherapy for standard risk hepatoblastoma (SR-HB)

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Background and rationale

- **SR-HB is defined as tumor extension limited to PRETEXT I, II or III, no involvement of portal or hepatic veins, no intra-abdominal extrahepatic disease, AFP >100ng/ml and no metastases, defined by CT scan.**
- **In SIOPEL 2 and 3, children were treated with a cumulative dose ranging from 320mg/m² to 560 mg/m², and audiology was carefully monitored. Results showed that 60% of children had permanent high-frequency hearing loss of Brock grade ≥1. Sodium thiosulfate (STS) may reduce the risk of ototoxicity. There are however concerns that STS could reduce the anti-tumor efficacy of cisplatin.**
- **When, as in standard risk hepatoblastoma, there is a survival rate of over 90% and operable disease at diagnosis, plus a tumor marker permitting safe and reliable monitoring of disease, then testing new drugs which could prevent ototoxicity becomes very important for the quality of life of the patients.**

Objectives and endpoint

- **To assess efficacy of STS to reduce hearing impairment caused by Cisplatin**
- **To carefully monitor potential impact of STS on response to Cisplatin and OS**

Primary endpoint: centrally reviewed absolute hearing threshold, at the age of ≥3.5 yrs, by pure tone audiometry, graded by Brock criteria

Secondary endpoints: response, resection, EFS, OS and long term renal function

Methods

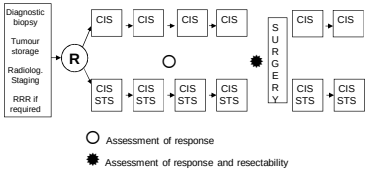
Treatment:

- **Newly diagnosed patients with SR-HB are treated with 4 chemotherapy courses every 2 weeks before surgery plus 2 courses after surgery.**
- **Patients are randomly assigned to receive Cisplatin alone or Cisplatin followed by STS. Cisplatin at a dose of 80mg/m² is administered i.v. over 6 hrs.**
- **STS is administered i.v. 6 hrs after stopping Cisplatin, over 15 mins, at 20g/m².**
- **Serum sodium is monitored 1 hr, 6 hrs and 18 hrs post STS.**

Tumor response:

- **Assessed after 2 and 4 cycles preoperatively with serum AFP (1 log fall, stricter criteria than previous SIOPEL trials) and liver imaging (any reduction in size)**
- **Any rise in AFP: stop STS and add doxorubicin**

Trial Design



Statistical consideration for sample size:

Objective: detect a reduction in hearing loss from 60% in the control arm to 35% in the experimental arm with a significance level of 5% and power of 80%. Two interim and one final analysis are planned with early stopping for efficacy. 102 fully evaluable patients are needed.

Patient Characteristics

45 sites from 11 countries recruited 113 pts; 109 are evaluable

	CIS N=52	CIS+STS N=57	Total N=109
Age (months): median	13.4	12.8	13.0
Gender: m	23 (44%)	27 (47%)	50
f	29 (56%)	30 (53%)	59
AFP (ng/ml): median	81,931	154,638	130,955
range	187 – 24.7×10⁶	273 – 4.5×10⁶	187 – 24.7×10⁶
1st - 3rd quartile	24,502 – 502,827	20,000 – 600,000	21,300 – 554,100
PRETEXT: I	0	11 (19%)	11
II	31 (60%)	30 (53%)	61
III	21 (40%)	16 (28%)	37

Early Efficacy and Tolerability Results

Efficacy		CIS N=52	CIS+STS N=57
Response after 2 cycles	PR	26 (50.0%)	23 (40.4%)
	SD	25 (48.1%)	34 (59.6%)
	n.a.	1 (1.9%)	0
Response after 4 cycles	PR	40 (76.9%)	40 (70.2%)
	SD	6 (11.5%)	13 (22.8%)
	PD	3 (5.7%)	3 (5.3%)
	n.a.	3 (5.7%)	1 (1.8%)
Status at end of treatment	CR	44 (84.6%)	52 (91.2%)
	PR	3 (5.8%)	4 (7.0%)
	PD	2 (3.9%)	0
	Died 1)	1 (1.9%)	0
	n.a.	2 (3.9%)	1 (1.8%)
Status at last follow up	CR	48 (92.3%)	52 (91.2%)
	Non-CR	1 (1.9%)	3 (5.3%)
	Died	3 (5.8%)	1 (1.8%)
	n.a.	0	1 (1.8%)

1) Died from surgical complications
n.a. = not available

Grade 3 and 4 Acute Toxicities		CIS N=52	CIS+STS N=57
Allergy	3	1 (1.9%)	0
Febrile neutropenia	3	4 (7.7%)	5 (8.8%)
Infection	3	5 (9.6%)	6 (10.5%)
Hypomagnesemia	3	1 (1.9%)	1 (1.8%)
Hypernatremia	3	0	1 (1.8%)
Vomiting	3	1 (1.9%)	3 (5.3%)
Nausea	3	3 (5.8%)	2 (3.5%)
Left ventricular systolic disfunct.	3,4	0	0
Other toxicities	3	14 (26.9%)	20 (35.1%)
	4	3 (5.8%)	5 (8.8%)

Other G3/4 toxicities encompass: hematological, liver and other biochemistry parameters

19 patients (CIS: 9; CIS+STS: 10) received between 1 and 6 courses of additional doxorubicin for varying reasons.

4 patients randomized to CIS+STS did not receive STS due to logistical problems.

Audiology Assessment

Most patients are too young after the end of treatment to have a definitive audiometric evaluation by pure tone audiometry (PTA). Therefore, the definitive evaluation is scheduled at the age of 3.5 years. Grading is with Brock criteria using the better ear to grade bilateral high-frequency hearing loss:

Bilateral hearing loss	Grade	Designation
< 40 dB at all frequencies	0	Minimal
≥ 40 dB at 8,000 Hz only	1	Mild
≥ 40 dB at 4,000 Hz and above	2	Moderate
≥ 40 dB at 2,000 Hz and above	3	Marked
≥ 40 dB at 1,000 Hz and above	4	Severe

Two interim analyses and one final analysis were planned after 34 and 68 patients were evaluable for the primary end point, and final analysis upon definitive audiology assessment of 102 patients. The first interim analysis was done in January 2015; the IDMC recommended to continue the trial as planned.

Conclusions

- **This randomised phase III trial shows that it is safe to treat standard risk hepatoblastoma with six cycles of Cisplatin monotherapy with the addition of the chemoprotectant Sodium Thiosulphate, provided that protocol instructions to add doxorubicin and stop STS in the case of a rise in AFP during treatment are followed.**
- **The response to 4 cycles of pre-operative chemotherapy and the status at end of treatment are comparable. The number of children developing progressive disease or receiving additional doxorubicin is equivalent.**
- **The final analysis of the audiological end point of this trial is expected in approximately 2 years when all children will have reached 3.5 years of age.**

Database support:

CINECA, Bologna, Italy

Pharma Company Support:

Fennec Pharma provided STS free of charge as clinical trial supply worldwide.

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