Sodium thiosulfate for prevention of hearing loss in children receiving cisplatin chemotherapy

SUMMARY

Sodium thiosulfate is intended to be used to prevent hearing loss in children who receive cisplatin chemotherapy. It inactivates platinum complexes by binding electrophilic platinium with thiol, thus forming a covalent complex that is not cytotoxic and can be excreted rapidly. Sodium thiosulfate does not currently have Marketing Authorisation in the EU for any indication.

Cancer in children (aged 0-14 years) is rare compared with the adult population, accounting for less than 1% of all cancers. Cisplatin is a widely-used chemotherapeutic agent and is standard of care for a variety of paediatric malignancies. All children who receive cisplatin are at risk of cisplatin-induced hearing loss, and it occurs in at least 60% of treated patients. Hearing loss is likely to delay speech and language development in children and can have a significant impact on school performance and psychosocial functioning.

There are currently no treatment options available to prevent hearing loss in children receiving cisplatin chemotherapy. Sodium thiosulfate is currently in phase III clinical trials investigating its effect on hearing loss when administered alongside cisplatin chemotherapy. These trials are expected to complete in late 2015 and late 2017.
TARGET GROUP

- Prevention of hearing loss in children receiving cisplatin chemotherapy.

TECHNOLOGY

DESCRIPTION

Sodium thiosulfate is a chemoprotectant/antioxidant intended to prevent hearing loss in children who receive cisplatin chemotherapy. It inactivates platinum complexes by binding electrophilic platinum with thiol, thus forming a covalent complex that is not cytotoxic and can be excreted rapidly. In clinical trials\(^1\), sodium thiosulfate was administered over 15 minutes at up to 20g/m\(^2\), exactly 6 hours following completion of cisplatin infusion.

Sodium thiosulfate does not currently have Marketing Authorisation in the EU for any indication. It is listed in the British National Formulary as an emergency treatment for cyanide poisoning\(^2\).

INNOVATION and/or ADVANTAGES

If licensed, sodium thiosulfate will provide a treatment option for this patient group for whom there are currently no curative or preventative treatments available.

DEVELOPER

Fennec Pharmaceuticals.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Cisplatin is a widely-used chemotherapeutic agent and is standard of care for a variety of paediatric malignancies, including osteosarcoma, neuroblastoma, medulloblastoma, hepatoblastoma and germ cell tumours\(^3,4\). However, one of the most important adverse effects is the occurrence of hearing loss (ototoxicity), which is characterised by bilateral, high frequency sensorineural hearing loss, and is often accompanied by tinnitus and vertigo\(^3,5\). It is permanent and occasionally has delayed onset, with progressive loss occurring many years after completion of therapy\(^6\). The hearing loss is caused by sensory hair cell destruction that begins at the base of the cochlea, where high frequency sounds are processed, and continues toward the cochlear apex, where lower frequency sounds are affected\(^6\). Hearing loss is likely to delay speech and language development in children and can have a significant impact on school performance and psychosocial functioning\(^6,7\).
NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:


CLINICAL NEED and BURDEN OF DISEASE

Cancer in children (aged 0-14 years) is rare compared with the adult population, accounting for less than 1% of all cancers. In England, the average number of new cases per year between 2009 and 2011 was 1,328, representing a World age-standardised incidence rate of around 145 per million population. All children receiving cisplatin are at risk of cisplatin-induced ototoxicity, and it occurs in at least 60% of paediatric patients. However, incidence varies according to patient group, dose received, patient age, and the criteria by which hearing impairment is defined, with reported rates ranging from 13-96%. The population likely to be eligible to receive sodium thiosulfate could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


Other Guidance


CURRENT TREATMENT OPTIONS

There are currently no treatment options available to prevent loss of hearing in children receiving cisplatin chemotherapy. Co-treatment with other potentially ototoxic drugs, cranial irradiation, age of <5 years and male sex increases the risk of cisplatin-induced ototoxicity. The dose and dosing schedule is also a risk factor, with high cumulative dose, high dose per

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*a Expert personal opinion.*
course and bolus application being high risk, although a threshold has not been identified below which cisplatin-induced ototoxicity is absent\(^3\).

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>SIOPEL 6, NCT00652132, CCLG-LT-2007-03, CDR0000590649, EU-20833, EUDRACT-2007-002402-21, SIOP-CCLG-LT-2007-03; children aged up to 18 years; sodium thiosulfate with cisplatin vs cisplatin; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Children’s Cancer and Leukaemia Group.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Abstract(^1), trial registry(^{17}), manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), Australia, New Zealand and Japan.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=113 (planned); aged over 1 month and less than 18 years; hepatoblastoma; stage I, II, or III; no prior chemotherapy.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to cisplatin with or without sodium thiosulfate given 6 hours after completion of cisplatin infusion. For all patients: Pre-surgery: 4 courses on days 1, 15, 29 and 43. Post-surgery: as soon as possible, but within 21 days – 2 courses on days 1 and 15. For children &gt;10kg, cisplatin, 80mg/m(^2) IV, with or without sodium thiosulfate, 20g/m(^2) IV; for infants and children 5-10kg, cisplatin, 2.7mg/kg IV, with or without sodium thiosulfate, 15g/m(^2); for infants &lt;5kg, cisplatin, 1.8mg/kg IV, with or without sodium thiosulfate, 10g/m(^2) IV. All cisplatin infusions over 6 hours, sodium thiosulfate infusions over 15 minutes.</td>
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<tr>
<td>Follow-up</td>
<td>Follow-up for at least 5 years.</td>
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<tr>
<td>Primary outcome</td>
<td>Rate of Brock(^b) grade ≥1 hearing loss.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Response to preoperative chemotherapy; complete resection; complete remission; event-free survival (EFS); overall survival (OS); toxicity; long-term renal clearance; feasibility of central audiology review.</td>
</tr>
<tr>
<td>Key results</td>
<td>-</td>
</tr>
<tr>
<td>Key results</td>
<td>For sodium thiosulfate/cisplatin and cisplatin, respectively: proportion of hearing loss (%), 28.6, 56.4 (p=0.004).</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>-</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>Not reported.</td>
</tr>
</tbody>
</table>

\(^b\) Brock scale (0-4), a validated grading system for cisplatin-related hearing loss.
ESTIMATED COST and IMPACT

COST

The cost of sodium thiosulfate is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Other:
- Reduced symptoms or disability
- No impact identified

Impact on Health and Social Care Services

- Increased use of existing services
- Re-organisation of existing services
- Other:
- Decreased use of existing services: potential for reduced outpatient, ENT and audiology visits.
- Need for new services
- None identified

Impact on Costs and Other Resource Use

- Increased drug treatment costs: additional treatment.
- Other increase in costs:
- Reduced drug treatment costs
- Other reduction in costs: potential for reduced use of educational and other supportive services, and reduced cost of hearing aids.
- None identified

Other Issues

- Clinical uncertainty or other research question identified:
- None identified

REFERENCES


