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Inhaled Lipid-complexed Cisplatin for pulmonary relapse of osteosarcoma

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LAY SUMMARY

Osteosarcoma is a rare cancer affecting the bones. It is also the most common bone cancer in children and young adults but can also occur in older adults. It mostly affects the knee, thigh bone, shin bone or upper arm. Symptoms include pain and swelling around the affected bone. Current treatment options have improved the prognosis of this disease, however, a recurrence of osteosarcoma may appear in other parts of the body after the primary cancer has been treated. The majority of the recurrences occur in the lungs. Symptoms of lung involvement may include cough, breathlessness, pain or discomfort in the chest.

Inhaled Lipid-complexed Cisplatin or inhaled liposomal cisplatin (ILC) is an anticancer drug being developed for the treatment of osteosarcoma that has reoccurred and spread to the lungs. Cisplatin is already available in the UK as an intravenous injection for treating multiple types of malignant conditions. ILC is administered via inhalation has the potential advantage to deliver the drug directly to the site of action (the lungs) with significantly reduced systemic side effects and toxicities. If licensed, ILC will offer an additional treatment option with the potential to improve effectiveness and safety for patients with pulmonary relapse of osteosarcoma.

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TARGET GROUP

Pulmonary metastasis in osteosarcoma (prevention of relapse after surgical remission; in adolescents)

TECHNOLOGY

DESCRIPTION

Inhaled Lipid-complexed Cisplatin or Inhaled Liposomal Cisplatin (ILC) is a novel, sustained release formulation of cisplatin in a nanoscale lipid based complex administered via inhalation.[1] Cisplatin is a platinum-based DNA synthesis inhibitor.[2] It works by three different mechanisms: 1) attachment of alkyl groups to DNA bases, resulting in the DNA being fragmented by repair enzymes in their attempts to replace the alkylated bases, preventing DNA synthesis and RNA transcription from the affected DNA, 2) DNA damage via the formation of cross-links (bonds between atoms in the DNA) which prevents DNA from being separated for synthesis or transcription, and 3) the induction of mispairing of the nucleotides leading to mutations.[3]

With ILC, local administration of cisplatin by inhalation has the ability to deliver the drug specifically to the site of action and therefore enhance the efficacy of the treatment, limit the penetration of nebulized therapeutic agent into the bloodstream and consequently decrease adverse systemic side effects.[4]

In the phase II trial (NCT01650090) of Inhaled Lipid Cisplatin in pulmonary recurrent osteosarcoma, patients received 36 mg/m2 (measured as concentration of cisplatin) of ILC intranasal via nebulization every two weeks for up to one year.[5]

Cisplatin has been licensed for multiple indications in the UK in its intravenous formulation such as in the treatment of testicular, lung, cervical, bladder, head and neck, and ovarian cancer (alone or in combination).[6] Frequently experienced side effects of cisplatin include, alopecia; bone-marrow suppression; extravasation; hyperuricaemia; hypomagnesaemia; myelosuppression; nephrotoxicity; oral mucositis; ototoxicity; peripheral neuropathy; severe nausea; severe vomiting; thromboembolism and tumour lysis syndrome.[6]

Cisplatin does not currently have Marketing Authorisation in the UK or EU for any indication in the inhaled liposomal form (as ILC).

INNOVATION and/or ADVANTAGES

Inhaled liposomal cisplatin (ILC) was designed to deliver high levels of sustained release cisplatin targeted to the lungs, without systemic-related toxicities.[3]

If licensed, ILC will offer an additional treatment option with the potential to improve effectiveness and safety for patients with pulmonary relapse of osteosarcoma.

DEVELOPER

Eleison Pharmaceuticals LLC.

REGULATORY INFORMATION/ MARKETING PLANS

Lipid complexed cisplatin is a designated orphan drug in the EU/USA for osteosarcoma.[7],[8]

PATIENT GROUP

BACKGROUND

Osteosarcoma is a rare bone cancer.[9] It is the most common primary malignant bone cancer in children and young adults,[10] however, it can also affect older adults.[11] It is defined as the primary malignant mesenchymal bone cancer where the malignant cancer cells directly form the osteoid or bone or both.[12] It mostly affects the knee, thigh bone, shin bone or upper arm. Osteosarcoma consists of 30% of all bone sarcoma diagnoses.[11] Osteosarcoma are classified as primary and secondary. Primary are further sub-typed as intramedullary/central and surface osteosarcomas.[12]

There has been a lot of research into the causes of osteosarcoma but a definite cause is unknown. There are a few risk factors that have been associated with osteosarcoma. Children who have hereditary retinoblastoma have an increased risk of developing osteosarcoma. Children who have previously had radiotherapy and chemotherapy also have an increased risk of developing osteosarcoma. Pain in the affected bone is the most common symptom. There may also be swelling around the affected bone.[13]

Many patients with osteosarcoma are cured.[13] Treatment of osteosarcoma involves combined treatments (adjuvant and neoadjuvant chemotherapy plus surgery) which have greatly improved prognosis.[10] However, a recurrence of osteosarcoma may appear in other parts of the body after the primary cancer has been treated.

Recurrent osteosarcoma occurs in 30-50% of patients with initial localized disease and 80% of patients presenting with metastatic disease.[14] Between 50% and 75% of patients with recurrent osteosarcoma initially have lung involvement only.[15] Approximately 30–40% of patients with initially non-metastatic osteosarcoma eventually develop lung metastasis.[10] Symptoms of pulmonary involvement may include cough, breathlessness, pain or discomfort in the chest or pleural effusion.[16]

Favourable prognostic indicators in recurrent osteosarcoma include a longer disease-free interval from initial diagnosis to relapse, good histologic response to neoadjuvant chemotherapy in the primary tumour, a solitary lesion, and the ability to achieve a second complete surgical remission. For patients with pulmonary relapse, fewer nodules, unilateral involvement, complete surgical resection, and absence of pleural disruption are favourable prognostic factors.[15]

CLINICAL NEED and BURDEN OF DISEASE

The outcome of patients with recurrent osteosarcoma is generally poor, with long-term survival rates of ~20%.[15] The 5-year and 10-year post-lung metastases overall survival (PLM-OS) has been reported as 17% and 15%, respectively.[17]

According to the HES data, in 2016/17 there were 37 finished consultant episodes (FCEs), 36 admissions and 39 FCE bed days due to unspecified malignant neoplasm of bone and articular cartilage

of limb (ICD-10: 40.9).[18] 21,139 finished consultant episodes (FCEs), 19,329 admissions and 24,533 FCE bed days due to secondary malignant neoplasm of lung (ICD-10 code: C78.0).[18]

However, there are no population estimates for pulmonary relapse in osteosarcoma specifically. Therefore, the population likely to be eligible to receive inhaled liposomal cisplatin could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Cancer service guideline. Improving outcomes for people with sarcoma (CSG9). Published March 2006.
- NICE technology appraisal guidance. Mifamurtide for the treatment of osteosarcoma (TA 235). Published October 2011.
- NICE interventional procedure guidance. Microwave ablation for treating primary lung cancer and metastases in the lung (IPG469). November 2013.
- NICE interventional procedure guidance. Percutaneous radiofrequency ablation for primary or secondary lung cancers (IPG372). December 2010.

NHS ENGLAND and POLICY GUIDANCE

- NHS England 2013/14 NHS Standard Contract for Primary Malignant Bone Tumours Service (Adults and Adolescents). B12/S(HSS)/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. European Society for Medical Oncology. 2010.[19]

CURRENT TREATMENT OPTIONS

The management of recurrent osteosarcoma needs to take into account the timing of recurrence/metastases, number of metastases, and site of metastases. The treatment of recurrent osteosarcoma is primarily surgical in the case of isolated lung metastases. Complete removal of all metastases must be attempted, as the disease is otherwise almost universally fatal, while more than a third of patients with a second surgical remission survive for >5 years. Even patients with multiple recurrences may be cured as long as recurrences are resectable, and repeated thoracotomies are often warranted. CT scan can both over- and underestimate the number of metastases. The role of second-line chemotherapy for recurrent osteosarcoma is much less well defined than that of surgery and there is no accepted standard regimen.[19]

At the moment, there are no NICE guidelines for the management of recurrent osteosarcoma with metastasis in the lungs. NICE guidance regarding primary or secondary lung cancers states the treatment depends mainly on tumour histology and stage, and may include:[20]

- Surgical resection (open or thoracoscopic)
- External beam radiotherapy,
- Chemotherapy
- Combination of these treatments

If the tumour protrudes into major airways, bronchoscopic treatments may include the following:[20]

- Diathermy
- Laser therapy
- Cryotherapy
- Brachytherapy
- Photodynamic therapy

Percutaneous RFA may be used in patients with small, early-stage lung cancers or small numbers of lung metastases who are unsuitable for, or prefer not to undergo, surgery.

EFFICACY and SAFETY	
Trial	NCT01650090, EP-ILC-201; 13 years and older; monotherapy for pulmonary relapse in osteosarcoma; phase II
Sponsor	Eleison Pharmaceuticals LLC
Status	Active, not recruiting
Source of Information	Trial registry[5]
Location	United States
Design	Open label, single group assignment
Participants	n=50 (planned); 13 years and older; history of osteosarcoma metastatic to the lung(s). Patients currently in surgical complete remission (CR) following one or two prior relapses of osteosarcoma involving pulmonary disease
Schedule	Patients will receive 36 mg/m2 (measured as concentration of cisplatin) of ILC via nebulization every two weeks for up to one year.
Follow-up	Active treatment for 1 year, follow-up 5 years
Primary Outcomes	Observed Relapse Free Interval (RFI) [Time Frame: At relapse, estimated at 6-12 months average]
Secondary Outcomes	• Median, 1, 2 and 5 year Overall Survival (OS) [Time Frame: 1, 2 and 5 Years] • Median, 1, 2 and 5 year Event Free Survival (EFS) [Time Frame: 1, 2 and 5 years]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Previously reported as June 2016

ESTIMATED COST and IMPACT

COST

The cost of ILC is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other:

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other:

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs:

☐ Other reduction in costs:

☒ Other:

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified:

☒ None identified

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