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HEALTH TECHNOLOGY BRIEFING
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MXT110 for newly-diagnosed diffuse intrinsic pontine glioma

NIHRIO ID	12421	**NICE ID**	10100
Developer/Company	Midatech Ltd	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase I/II trial.

SUMMARY

MTX110 is in clinical development for newly-diagnosed diffuse intrinsic pontine glioma (DIPG). DIPG is a high grade childhood brain tumour. The cause is unknown. DIPG develops in a part of the brain stem known as the pons, which controls essential body functions including heartbeat, breathing, eyesight and balance. The symptoms of DIPG may include; abnormal alignment of the eyes, arm and leg muscle weakness, unstable balance and speech difficulties. Because the tumour grows amongst normal nerves cells of the brain stem, it is difficult to treat as they are not surgically resectable. Radiotherapy can temporarily slow the tumour's growth but is not curative and chemotherapy is often ineffective.

MTX110 contains the anticancer drug panobinostat, which works by inhibiting an enzyme that increases the division and growth of cancer cells. Orally administered panobinostat cannot cross the blood brain barrier and its use in treating DIPG is currently limited. MTX110 contains a special formulation of panobinostat that enables the direct delivery of high concentrations of panobinostat by infusion to tumour sites, which bypasses the blood-brain barrier. This is expected to improve both the safety and efficacy of the treatment while reducing the potential for toxicity and other side effects.

PROPOSED INDICATION

Newly-diagnosed diffuse intrinsic pontine glioma (DIPG).[1]

TECHNOLOGY

DESCRIPTION

MTX110 (panobinostat nanoinclusion complex) contains panobinostat as the active ingredient.[2] Panobinostat is a histone deacetylase (HDAC) inhibitor that inhibits the enzymatic activity of HDACs at nanomolar concentrations. HDACs catalyse the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. Inhibition of HDAC activity results in increased acetylation of histone proteins, an epigenetic alteration that results in a relaxing of chromatin, leading to transcriptional activation. In vitro, panobinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Panobinostat shows more cytotoxicity towards tumour cells compared to normal cells.[3]

MTX110 is lyophilised and reconstituted to an aqueous liquid form to deliver panobinostat parenterally in liquid form via convection enhanced delivery (CED). This increases available routes of administration for panobinostat as the drug does not cross the blood-brain barrier effectively when given orally. This technique allows for high drug concentrations to be delivered to the tumour while simultaneously minimising systemic toxicity and other side effects.[2]

MTX110 is in clinical development for the treatment of newly-diagnosed diffuse intrinsic pontine glioma (DIPG). In the phase II clinical trial (NCT03566199), MTX110 is administered via CED infusion on day 1 or days 1 and 2 as determined by dose level. This will be repeated every 4-8 weeks for up to 24 months in the absence of disease progression or unacceptable toxicity. The treatment dosage was not reported.[1]

INNOVATION AND/OR ADVANTAGES

DIPGs are lethal high-grade paediatric brain tumours that are inoperable and without cure. Despite numerous clinical trials, the prognosis remains poor. Systemic administration of chemotherapeutic agents is often hindered by the blood brain barrier (BBB), and even drugs that successfully cross the barrier may suffer from unpredictable distributions.[4] Panobinostat was highlighted by DIPG experts as a potentially important treatment from a targeted preclinical screening program.[5]

Panobinostat has been found to be an efficacious and clinically available drug against DIPG in vitro but oral dosing may cause unacceptable systemic toxicity and does not penetrate the central nervous system (CNS) in humans, which means that it is of considerable interest as a treatment for DIPG when administered by CED. CED represents a method of direct intraparenchymal administration of drug to the brain via surgically implanted microcatheters. By infusing at precisely controlled, low infusion rates, a drug can be distributed over a large volume into brain by bulk flow, displacing the extracellular fluid with infusate. However, the ability of CED of panobinostat is limited by its poor water solubility. Drugs need to be water soluble at physiological pH to be delivered to the brain by CED.[6]

To overcome these challenges, MTX110 is formulated as a parenteral solubilised form of panobinostat delivered directly into the tumour under slight pressure via CED. This thus

bypasses the blood-brain barrier and is expected to improve both the safety and efficacy of the treatment while reaching the tumour site in high therapeutic concentrations and simultaneously minimising systemic toxicity and other side effects.[6,7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

MTX 110 does not currently have Marketing Authorisation in the EU/UK for any indication.

PATIENT GROUP

DISEASE BACKGROUND

Childhood brain stem glioma is a rare condition in which abnormal cells develop in the tissues of the brain stem (the part of the brain connected to the spinal cord). The condition can be benign (noncancerous) or malignant (cancerous). Diffuse intrinsic pontine glioma (DIPG) is a subtype of childhood brain stem glioma.[8]

DIPGs are paediatric highgrade gliomas (pHGG) characterised by infiltrative tumours of the brainstem. DIPGs are histologically astrocytomas, have a peak onset of 6–9 years (adolescents and adults can also be affected) and account for 10–20% of all paediatric brain tumours.[9] A number of genetic, epigenetic and molecular profiles of these tumours have been identified, and mutation of a gene called H3K27M has been associated with an increased risk of developing a diffuse midline glioma. However, the fact that these tumours consist of a number of different types of damaged cells in varying proportions between patients makes it very difficult to identify any one cause. There are two rare genetic conditions that can be inherited and are associated with a higher risk of developing these types of tumours: Li-Fraumeni syndrome and neurofibromatosis type 1.[10]

Because DIPG progresses rapidly, children typically experience symptoms for a month or less before they are diagnosed.[11] The diagnosis of DIPG is based on the clinical history and examination combined with radiographic findings.[11] DIPGs present with a constellation of symptoms including headache, nausea, cranial nerve dysfunction, facial and extremity weakness, impairments of gait, coordination or speech cerebellar signs, and long tract sings, with some patients demonstrating hydrocephalus. Prognosis of these tumours remains uniformly poor, with a median survival of around 1 year from the time of diagnosis despite extensive efforts to improve this. Patients eventually develop worsening neurologic deficits, brainstem dysfunction, and hydrocephalus, before ultimately succumbing to their disease.[4,9]

CLINICAL NEED AND BURDEN OF DISEASE

DIPG is one of the deadliest paediatric CNS cancers, accounting for the majority of deaths secondary to brain tumours in this age group.[12] DIPG accounts for approximately 75% to 80% of paediatric brain stem tumours.[13]

Characteristics associated with longer survival include younger age, longer symptom latency, and absent ring enhancement on diagnostic magnetic resonance imaging.[14]

Radiation is the only treatment with proven efficacy in prolonging progression-free survival (PFS). There are currently no proven chemotherapeutic agents that have been shown to increase PFS or overall survival.[9]

The majority of children with DIPG unfortunately succumb to their disease within a short time despite treatment with radiotherapy. During their illness trajectory, these children suffer from multiple symptoms, including pain, fatigue, depression, nausea and vomiting, seizures and other neurologic deficits.[12]

Approximately 4% of children with DIPGs are diagnosed when younger than 3 years. The prognosis of these children is more favorable than that of older children, with 28% of younger children alive at 2 years following diagnosis compared with 8% of children aged 3 to 10 years at diagnosis and 14% of children older than 10 years at diagnosis. The more favorable prognosis for young children may reflect the presence of different biological characteristics in different age groups.[13]

Longer duration of symptoms is associated with a more favorable prognosis. The median survival for children with DIPGs is less than 1 year, although about 10% of children will survive longer than 2 years. Two-year survival rates range from 7% for patients with duration of symptoms less than 6 months to 29% for patients with duration of symptoms of 24 months or longer. [13]DIPG affects between 20 to 30 children in the UK every year.[15]

In England, in 2017 there were 260 (19 cases under 1 year, 91 cases in 1-4 years, 87 cases in 5-9 years and 63 cases in 10-14 years) registrations of newly diagnosed cases and of malignant neoplasm of brain (ICD-10; C71) in children between the age of 0 and 14 years.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Because DIPG grows diffusely and infiltrates critical brainstem structures, surgical resection is not possible. Radiation therapy has remained the mainstay of treatment. Radiotherapy provides temporary improvement or stabilization of symptoms and extends overall survival by an average of 3 months; median survival is less than 5 months without radiation. Though both clinical and radiographic responses are initially observed, local recurrence invariably occurs.[11]

To date, no chemotherapeutic strategy has been shown to improve overall survival in children with DIPG, including neoadjuvant chemotherapy, chemoradiotherapy, adjuvant chemotherapy, chemotherapy initiated at the time of clinical or radiologic progression post radiation, or high-dose therapy with stem cell rescue.[17]

CURRENT TREATMENT OPTIONS

Treatment usually consists of standard fractionated radiation to a dose of 54-59 Gy (over 30 fractions).[4]

PLACE OF TECHNOLOGY

If licensed, MTX110 will offer a treatment option for patients with DIPG who currently have no effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	NCT03566199, **PNOC015; children and adults aged 2-21 years; MTX110; phase I/II**
Sponsor	Sabine Mueller, MD, PhD
Status	Ongoing
Source of Information	Trial registry[1]
Location	USA
Design	Open label; single group treatment
Participants	N= 24 (planned); aged 2-21 years; patients with newly diagnosed DIPG by magnetic resonance imaging (MRI)
Schedule	Participants will receive MTX110 by CED infusion on day 1 or days 1 and 2 as determined by dose level. Courses repeat every 4-8 weeks
Follow-up	Up to 24 months in the absence of disease progression or unacceptable toxicity.
Primary Outcomes	Safety of repeated convection-enhanced delivery (CED) of MTX110 following standard of care focal radiotherapy [Time frame: up to 5 years]
Secondary Outcomes	Overall survival at 12 months [Time frame: up to 12 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as September 2019

ESTIMATED COST

The cost of MTX110 is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- No NICE guidance identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No NHS England guidance identified

OTHER GUIDANCE

- European Association for Neuro-Oncology (EANO). EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. 2014.[18]

ADDITIONAL INFORMATION

Midatech did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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