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Belinostat (Beleodaq) with CHOP for treatment of patients with peripheral T-cell lymphoma, 1st line

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LAY SUMMARY

Peripheral T-cell lymphoma (PTCL) is a rare form of lymphoma, a cancer affecting a type of white blood cell called a lymphocyte. At the beginning, the symptoms of lymphoma can be very varied and difficult to diagnose, but as the lymph nodes get bigger, a painless swelling in the neck, armpit or groin is sometimes noticed. The condition generally affects people aged over 60 years of age and it is slightly, more common in men than in women. By the time they are diagnosed, the lymphoma has often spread widely around the body. The main treatment is chemotherapy, but not all patients are well enough to manage this and the disease often returns after treatment.

Belinostat is a new drug under development for the treatment of peripheral T-cell lymphoma. The safety and efficacy of belinostat is currently being evaluated for use in combination with traditional front-line chemotherapies for the treatment of PTCL. Belinostat is given as a single injection in a dosing regimen that involves a 21-day cycle.

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TARGET GROUP

Peripheral T-cell lymphoma – first line; in combination with CHOP (cyclophosphamide + doxorubicin + vincristine + prednisolone)

TECHNOLOGY

DESCRIPTION

Belinostat (Beleodaq, PXD101, PX105684) is a novel agent that inhibits the enzyme histone deacetylase (HDAC) with a sulfonamide-hydroxamide structure. The safety and efficacy of belinostat is currently being evaluated for use in combination with traditional front-line therapies for the treatment of peripheral T-cell lymphomas (PTCL). Intravenous administration of the agent is available as Beleodaq as monotherapy and the dosing regimen involves a 21-day cycle.[1]

Belinostat for the treatment of PTCL was approved in the USA in July 2014 as a therapeutic agent for relapsed or refractory peripheral T-cell lymphoma.[2]

In the UK there are no specific treatments for PTCL, the disease is treated in the same way as the broader class of lymphomas known as non – Hodgkin's lymphomas.[3,4] According to NICE, for the management of PTCL at first line CHOP (cyclophosphamide + doxorubicin + vincristine + prednisolone) chemotherapy should be considered.[4]

A phase III trial is planned and estimated to have started in 2016[5] to assess the efficacy of belinostat in combination with the CHOP treatment, against CHOP in the 1st line of treatment of peripheral PTCL.[6] The proposed dose of belinostat is 1000mg/m^2 given on days 1 to 5 of a 21-day cycle.[7]

Belinostat does not currently have marketing authorization in the EU for any indication. Recently, a Managed Access programme has been launched in Europe for patients with PTCL. The programme allows physicians to request belinostat for individual patients for whom alternative treatment options are not currently available. This enables patients on a named patient basis in Europe (United Kingdom, Germany, France, Spain, Italy, Denmark, Sweden, Norway, Finland, Belgium, The Netherlands, Luxembourg, and Austria) to benefit from belinostat treatment ahead of a potential European approval.[8]

INNOVATION and/or ADVANTAGES

If approved, belinostat in combination with CHOP will offer an additional treatment option for patients with PTCL for whom the outcome of frontline chemotherapy regimens has been poor, with reported long-term survival of only 20 to 30%.[9] Belinostat has the potential to improve safety, in comparison to other histone deacetylase inhibitors (pralatrexate, romidepsin, brentuximab vedotin).[9]

DEVELOPER

Onxeo DK and Spectrum Pharmaceuticals.

AVAILABILITY, LAUNCH or MARKETING

In the EU, belinostat has been designated orphan drug for the treatment of PTCL[10] and malignant thymoma.[11]

Belinostat was awarded Accelerated Approval status, Fast Track Designation, Orphan Drug Designation and Priority Review Designation by the FDA in July 2014.[12]

Beleodaq is approved and commercialized in the USA and is licensed in some Latin American countries (not specified).[a]

The company has not disclosed available information regarding plans for marketing authorisation application in the UK.

PATIENT GROUP

BACKGROUND

Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). Lymphoma occurs when lymphocytes grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a tumour.[13]

The body has two main types of lymphocytes that can develop into lymphomas: B-lymphocytes (B-cells) and T-lymphocytes (T-cells). Peripheral T-cell lymphoma (PTCL) consists of a group of rare and usually aggressive NHLs that develop from mature T-cells. Most T-cell lymphomas are PTCLs.[13]

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of mature T-cell lymphomas.[9] Different types of peripheral T-cell lymphoma have been identified and categorised as nodal, other extranodal and leukaemic or disseminated.[10]

The symptoms of the disease vary according to the type of lymphoma, but the initial symptom is usually a lump in the neck, under the arm or in the groin area, which is caused by an enlarged lymph node. The lymphoma may also affect other organs in the body such as the bone marrow, liver and the skin. PTCL is a long-term debilitating and life-threatening condition because in most cases the disease does not respond well to therapy, reoccurs within a year following initial treatment and is associated with poor overall survival.[10]

CLINICAL NEED and BURDEN OF DISEASE

In 2014, more than 13,000 people were diagnosed with non-Hodgkin's lymphoma in the UK.[14] It is estimated that around 10% of non-Hodgkin's lymphoma is classified as PTCL.[15] It generally affects people over 60 years of age and incidence is slightly higher in men then in women.[15]

Approximately 4,800 people died of this condition in 2014. An estimated 7 in 10 (69%) of people diagnosed with non-Hodgkin's lymphoma in England and Wales survive their disease for five years or

[a] Information provided by company

more (2010-11). Survival is similar in men than women; the survival rate is improving and has tripled in the last 40 years in the UK.[14]

In 2015/206 Hospital Episodes Statistics there were a total of 106,900 finished consultant episodes (FCE), 99,191 admissions and 170,354 FCE bed days registered for follicular lymphoma, non-follicular lymphoma, Mmture T/NK-cell lymphomas, other and unspecified types of non-Hodgkin's lymphoma, and other specified types of T/NK-cell lymphoma (ICD-10 codes C82 to C86).[16]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. T-cell lymphoma (peripheral, relapsed or refractory) - romidepsin [ID504] (GID-TAG433). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Lymphoma (non-Hodgkin's, peripheral T-cell) - pralatrexate [ID368] (GID-TAG424). Expected of issue to be confirmed.
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.
- Department of Health. Improving Outcomes: A Strategy for Cancer (2011). 12 January 2011

OTHER GUIDANCE

British Committee of Standards in Haematology. *Guideline for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell Lymphoma).* Updated August 2013.[17]

CURRENT TREATMENT OPTIONS

In the UK, the current treatment option for peripheral T-cell lymphoma is CHOP chemotherapy as first line with the possibility of consolidation therapy with autologous stem cell transplantation for people with chemo sensitive peripheral T‑cell lymphoma (that is, there has been at least a partial response to first‑line chemotherapy) who are fit enough for transplantation.[4]

The chemotherapy regimen would include cyclophosphamide, doxorubicin, vincristine and prednisolone.[4]

EFFICACY and SAFETY

Trial	NCT01839097; phase I
Sponsor	Spectrum Pharmaceuticals, Inc
Status	Complete and published[9]

Source of Information	Trial register [18]
Location	USA
Design	Single arm
Participants	N= 23 adults diagnosed with PTCL with life expectancy of more than 3 months
Schedule	Belinostat will be administered by intravenous infusion once daily for up to 5 days depending on the dose cohort as follows: Cohort 1: belinostat 1000 mg/m2 IV on Day 1 Cohort 2: belinostat 1000 mg/m2 IV on Day 1-2 Cohort 3: belinostat 1000 mg/m2 IV on Day 1-3 Cohort 4: belinostat 1000 mg/m2 IV on Day 1-4 Cohort 5: belinostat 1000 mg/m2 IV on Day 1-5 Cyclophosphamide - 750 mg/m2 - IV - Day 1 Vincristine - 1.4 mg/m2 - IV - Day 1 Doxorubicin - 50mg/m2 - IV - Day 1 Prednisone 100mg PO - On Day 1 Prednisone will be administered after chemotherapy part of CHOP, and on Day 2-5 after belinostat.
Follow-up	126 days
Primary Outcomes	To determine the maximum tolerated dose (MTD) for belinostat when combined with CHOP regimen and establish the phase 3 recommended belinostat dose.
Secondary Outcomes	Safety and tolerance (up to 5 days); overall response rate (ORR) after 6 cycles of BelCHOP regimen; pharmacokinetics of belinostat when co-administered with CHOP regimen.
Key Results	Results outlined in the oral presentation of results showed an ORR of 86% with the belinostat and CHOP combination, based on 21 evaluable patients (18/21), with the vast majority, 67%, achieving a complete response (14/21), and 19% achieving a partial response (4/21). In addition, the belinostat and CHOP combination was shown to have an acceptable safety profile with no new or unexpected toxicities.[19]
Adverse effects (AEs)	The most common (> 10%) Grade 3-4 hematologic adverse events (AEs) reported with Bel-CHOP were as expected: neutrophil count decreased (30%), anemia (22%), neutropenia (22%), white blood cell (WBC) count decreased (22%), febrile neutropenia (17%) and lymphocyte count decreased (17%). No Grade 3-4 non-hematologic AEs > 10% were reported. No patient discontinued therapy due to AEs. One patient died as a result of disease progression during the study. [19]
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of belinostat in combination with CHOP (BelCHOP) chemotherapy 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: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

Onxeo

Onxeo 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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