CPX-351 (VYXEOS) for elderly patients with newly diagnosed acute myeloid leukaemia – first line

LAY SUMMARY

Acute myeloid leukaemia is a rare type of cancer that affects the way blood cells are developed so that they do not work properly. This leads to an increased risk of infection, as well as symptoms such as anaemia and bruising. It can affect people at any age but is more common in people over 65.

Chemotherapy drugs can be very effective in the treatment of acute myeloid leukaemia. In some situations, these drugs are combined with stem cell or bone marrow transplant to improve the chances of curing the leukaemia. However, some patients cannot tolerate intensive chemotherapy and non-intensive treatments are offered.

CPX-351 is a new product aimed at patients aged 60 years or older which delivers two of the most commonly used drugs in the treatment of acute myeloid leukaemia (cytarabine and daunorubicin) in a new combination.

If CPX-351 is licensed for use in the UK, it could be a new treatment option for these patients. A current trial is looking to see whether CPX-351 can improve survival compared to an existing treatment, and whether it is safe to use.

NIHR HSRIC ID: 5693
TARGET GROUP

- Acute myeloid leukaemia: patients ≥60 years of age; newly diagnosed; high risk – first line.

TECHNOLOGY

DESCRIPTION

CPX-351 (VYXEOS; cytarabine: daunorubicin; cytarabine: daunorubicin liposomal injection; daunorubicin/cytarabine) is a liposomal encapsulated combination product incorporating cytarabine (an antimetabolic agent) and daunorubicin (an anthracycline antitumor antibiotic) in a 5:1 ratio. Existing treatment regimens for acute myeloid leukaemia (AML) include 7 days of standard-dose cytarabine, and 3 days of an anthracycline, such as daunorubicin or idarubicin ("3+7" regimen). CPX-351 delivers a fixed ratio of these two drugs in vitro.

CPX-351 is intended to be used as first line therapy for the treatment of newly diagnosed, high risk, AML in patients aged 60 years and older who are considered to be eligible for intensive therapy. CPX-351 is administered by intravenous (IV) infusion over 90 minutes. Patients are eligible to receive up to two induction and two consolidations, such that a full course of therapy may consist of four cycles of therapy (168-244 days). In the first induction cycle, CPX-351 is administered at 100units/m² on days 1, 3 and 5. The second induction, if required, is administered on days 1 and 3 at 100units/m². In both consolidation cycles, CPX-351 is administered at a reduced dose of 65units/m² on days 1 and 3. High-risk AML includes treatment-related AML, AML with antecedent haematological disorder, or de novo AML with myelodysplastic syndromes karyotype.

Cytarabine is currently licensed in the UK for the treatment of AML in adults and for other acute leukaemias in adults and children. Daunorubicin is currently licensed in the UK for the treatment of acute myelogenous and lymphocytic leukaemias and for the treatment of acute lymphocytic leukaemia and AML in children, as part of a combination regimen. In addition, liposomal daunorubicin (DaunoXome) is currently licensed for the treatment of advanced HIV-related Kaposi’s Sarcoma.

CPX-351 does not currently have Marketing Authorisation in the EU for any indication. CPX-351 is also in a phase II clinical trial for myelodysplastic syndrome.

INNOVATION and/or ADVANTAGES

If licensed, CPX-351 will offer an alternative treatment option for AML patients of 60 years of age and older, a group who currently have few (well tolerated) effective therapies available.

DEVELOPER

Celator Pharmaceuticals Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials CPX-351 is a designated orphan drug in the EU and USA.
PATIENT GROUP

BACKGROUND

AML is characterised by the overproduction of immature myeloid cells\(^3\). Due to the activation of abnormal genes through chromosomal translocations and other genetic abnormalities, there is maturation arrest of bone marrow cells in the early stages of development. The affected bone marrow begins to release a large number of immature white blood cells known as blast cells\(^4,5\). The immature cells occupy space in the marrow required for normal haematopoiesis, resulting in reduced number of neutrophils, platelets and erythrocytes\(^3,6\). Some less common types of AML may also be characterised by excess immature platelets or immature red blood cells\(^7\).

AML typically leads to an increased risk of infection, symptomatic anaemia, excessive bleeding, and other symptoms, which greatly reduce patient quality of life\(^4,3,8\). Other symptoms include fever, shortness of breath and bone pain. At diagnosis, most patients have a white blood cell count that is above normal and low neutrophil and platelet numbers\(^3\). Whilst the cause of AML is uncertain, known risk factors include exposure to high levels of radiation and exposure to benzene (a chemical used in manufacturing that is also found in cigarettes)\(^8\).

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

CLINICAL NEED and BURDEN OF DISEASE

AML is the most common malignant myeloid disorder in adults\(^9\). In England there were 2,856 cases of AML in 2012 (representing 9 cases per 100,000 population)\(^10\). The incidence of AML is slightly higher in males than in females (12:10)\(^10\) and is also related to age, with 40% of cases being in people aged 75 years and over\(^10\). In England and Wales there were 2,212 deaths from AML registered during 2014 (ICD-10 C92.0)\(^11\). In 2014-15, there were 40,475 hospital admissions for AML (ICD-10 C92.0) in England, resulting in 119,582 bed days and 43,022 finished consultant episodes\(^12\).

The proportion of patients with AML who are able to tolerate and thereby receive intensive chemotherapy could not be established from searches of routine, publicly available data sources, and therefore the population eligible to receive CPX-351 could not readily be established. However expert comment suggests that based on the AML 18 trial\(^13\), approximately one third of those above the age of 65 would be eligible\(^a\).

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\(^a\) Expert personal communication.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development: Leukaemia (acute myeloid, over 30% blasts) - azacitidine [ID829]. Expected July 2016.

Other Guidance

- European Society for Medical Oncology. Acute myeloblastic leukaemia in adult patients: ESMO Clinical recommendations for diagnosis, treatment and follow-up. 201014.

CURRENT TREATMENT OPTIONS

Guidelines recommend that the treatment of AML should be planned with curative intent whenever possible16. Azacitidine is currently recommended for the treatment of adult patients with AML with 20-30% blasts and multi-lineage dysplasia, who are not eligible for haematopoietic stem cell transplantation (HSCT) according to the World Health Organization (WHO) criteria17. Additionally, treatment of AML may be classified as either intensive or non-intensive; intensive chemotherapy is divided into an induction phase, followed by two courses of consolidation and (rarely) a maintenance phase14. Maintenance chemotherapy is not routinely administered outside of clinical trials for patients with non-acute promyelocytic leukaemia AML18. Potential candidates for allogeneic HSCT (alloHSCT) should be identified early at diagnosis or during induction chemotherapy14. AlloHSCT as a post-remission strategy is associated with the lowest rates of relapse18.

Intensive treatment is comprised of:

- Induction chemotherapy which may include an anthracycline and cytarabine (standard in UK is ‘3+10’ or ‘3+8’ regimen)b. Haematopoietic growth factors (such as granulocyte colony-stimulating factor [G-CSF] and granulocyte macrophage [GM]-CSF) are an optional adjunct to intensive induction chemotherapy14,18.
- Consolidation therapy is warranted once patients have reached clinical haematological remission. In good-risk AML patients in first remission who have a relapse risk of 35% or less, alloHSCT is not justified because its toxic effect and the risk of transplantation-related mortality exceeds the benefit. Good-risk AML patients, as well as patients who are unsuitable for alloHSCT for other reasons, should receive at least one cycle of intensive consolidation chemotherapy, preferably incorporating intermediate or high-dose cytarabine. Patients with AML in intermediate- and poor-risk groups with a human leukocyte antigen (HLA)-identical sibling may be candidates for alloHSCT. Patients in

b Expert personal communication.
these risk groups without a family donor may qualify for alloHSCT with an HLA-matched unrelated donor identified through an international donor registry. Conditioning regimens for alloHSCT with dose-reduced chemotherapy intensity may be used for patients in the upper age range (particularly those 50 years of age and older)\textsuperscript{18}.

Non-intensive treatment of AML is an important treatment option for patients with significant co-morbidity and the frail elderly, who are ineligible for conventional chemotherapy\textsuperscript{14}. Current non-intensive treatment options include low-dose cytarabine, which can induce haematological remissions in a small proportion of patients, best supportive care\textsuperscript{7} or entry into clinical trials of novel agents. Cytoreductive agents, such as hydroxyurea or low-dose cytarabine, may be used to reduce excessive leucocytosis\textsuperscript{6,14}. Treatment of infections due to neutropenia and transfusions to cover anaemia or thrombocytopenia are important additional measures. In severely neutropenic patients, haematopoietic growth factors may be considered when neutropenic fever or infections are a problem\textsuperscript{6,14}.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01696084, CLTR0310-301; CPX-351 vs cytarabine and daunorubicin (7+3); phase III.</th>
<th>NCT00788892, CLTR0308-204, 2009-010951-28; CPX-351 vs cytarabine and daunorubicin (7+3); phase IIb.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Celator Pharmaceuticals and The Leukaemia and Lymphoma Society.</td>
<td>Celator Pharmaceuticals.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Completed.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{1}.</td>
<td>Publication\textsuperscript{19}, trial registry\textsuperscript{2}.</td>
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<td>Location</td>
<td>USA and Canada.</td>
<td>USA and Canada.</td>
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<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
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<td>Participants</td>
<td>n=300 (planned); aged 60 to 75 years; newly diagnosed AML including therapy-related AML, AML with a history of myelodysplasia (MDS), AML with a history of chronic myelomonocytic leukaemia (CMMoL) and de novo AML with karyotypic abnormalities characteristic of MDS.</td>
<td>n=126; aged 60 to 75 years; pathological confirmation of AML; Eastern Cooperative Oncology Group (ECOG) performance status 0-2; serum creatinine &lt;2.0mg/dL, serum total bilirubin &lt;2.0mg/dL, serum alanine aminotransferase or aspartate aminotransferase &lt;50IU/L.</td>
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<td>Schedule</td>
<td>Patients randomised to IV CPX-351 at 100u/m\textsuperscript{2} on days 1, 3 and 5 by approximately 90 minute infusion; or IV cytarabine and daunorubicin (7 + 3) at 100mg/m\textsuperscript{2}/day cytarabine by continuous infusion for 7 days and 60mg/m\textsuperscript{2} daunorubicin on days 1, 2 and 3. Patients randomised for CPX-351 are eligible to receive up to 2 inductions and 2 consolidations, such that a full course of therapy may consist of 4 cycles of therapy. In the first induction cycle, CPX-351 is dosed at 100u/m\textsuperscript{2} on days 1, 3 and 5. The second induction, if required, is administered on days 1 and 3 at 100u/m\textsuperscript{2}. In both consolidation cycles, CPX-351 is administered at a reduced dose of 65u/m\textsuperscript{2} on days 1 and 3.</td>
<td>Patients randomised to IV CPX-351 at 100u/m\textsuperscript{2} on days 1, 3 and 5 by 90 minute infusion; or IV cytarabine and daunorubicin (7 + 3) at 100mg/m\textsuperscript{2}/day cytarabine by continuous infusion for 7 days and 60mg/m\textsuperscript{2} daunorubicin for 3 days.</td>
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Follow-up | Patients are eligible to receive up to 2 inductions and 2 consolidations. If a patient receives all four cycles, treatment would be between 168-224 days for a full course of CPX-351. Follow-up for 5 years from randomisation. | Patients are eligible to receive up to 2 inductions and 2 consolidations. If a patient receives all four cycles, treatment would be between 168-224 days for a full course of CPX-351. Follow-up for 2 years from randomisation.  

Primary outcomes | Overall survival (OS). | CR+CRi.  

Secondary outcomes | Safety; morphologic leukaemia free state; post-induction response (complete response [CR] + complete response with incomplete blood count recovery [CRi] according to morphologic, cytogenetic and molecular response); remission duration (relapse-free survival); event free survival (EFS); overall best post-treatment response (CR, CR+CRi); serum copper; pharmacokinetics; pharmacoeconomics, health economic endpoints. | Response duration; EFS; OS; survival at 2 years; rate of stem cell transplant up to 2 years from randomisation; early induction mortality at day 30 and at day 60 from start of 1st induction; late mortality following day 90 from 1st induction.  

Key results | - | For CPX-351 vs cytarabine and daunorubicin, respectively: CR, 48.8% vs 48.8%; CRi, 17.9% vs 2.4%; OS, 14.7 months vs 12.9 months; EFS, 6.5 months vs 2 months.  

Adverse effects (AEs) | - | Common AEs for the CPX-351 group included febrile neutropenia, infection, rash, diarrhoea, nausea, oedema and constipation. Two patients died of intracranial haemorrhage during CPX-351 consolidation (one of which was associated with head trauma and relapsed AML and the other as a result of chemotherapy-induced thrombocytopenia). By day 30, 3 of 85 (3.5%) CPX-351 patients had died; by day 60, 4 of 85 (4.7%) of patients had died compared with 7.3% and 14.6% in the cytarabine and daunorubicin arm, respectively.  

Expected reporting date | Primary completion date previously reported as November 2014. | -  

**ESTIMATED COST and IMPACT**

**COST**

The cost of CPX-351 is not yet known. Cytarabine is already licensed for use in the EU; a 5ml vial (20mg/ml) costs £3.90. Daunorubicin is also already licensed for use in the EU; a 20mg vial £55.00.
# IMPACT - SPECULATIVE

## Impact on Patients and Carers

- **☑ Reduced mortality/increased length of survival:** expert comment suggests that CPX-531 has shown effect in secondary AML and improved survival...60 day mortality is less than standard treatment. Additionally, improvement in CR rates were noted.
- **☐ Reduced symptoms or disability**
- **☑ Other:** experts suggest that toxicity e.g. febrile neutropenia and sepsis grade 3 and above, are higher with CPX-351.
- **☐ No impact identified**

## Impact on Health and Social Care Services

- **☐ Increased use of existing services**
- **☑ Decreased use of existing services:** expert comment suggests that fewer bed days are required.
- **☐ Need for new services**
- **☐ Other:**
- **☐ None identified**

## Impact on Costs and Other Resource Use

- **☑ Increased drug treatment costs:** expert comment highlights that there is an increased number of courses with CPX-351 (2 induction and 2 consolidations) versus standard chemotherapy (1 induction and 2 consolidations).
- **☐ Reduced drug treatment costs**
- **☐ Other reduction in costs:** expert comment notes that fewer individual doses are required (compared to the 3+10 dosing structure) and this would ease administration and reduce nursing time.
- **☐ Other increase in costs:**
- **☐ Other:**
- **☐ None identified**

## Other Issues

- **☑ Clinical uncertainty or other research question identified:** expert opinion suggests that patient bed days and quality of life data for CPX-351 would be useful. Current phase III trials may provide the answers but as it is a USA study, these issues may not be as pertinent to them.
- **☐ None identified**

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*Expert personal communication.*
REFERENCES


6 NIHR Horizon Scanning Centre. Azacitidine (Vidaza) for acute myeloid leukaemia – first line. University of Birmingham, September 2012. www.hsric.nihr.ac.uk


