Elacytarabine for relapsed or refractory acute myeloid leukaemia – second or third line

SUMMARY

Elacytarabine is intended to be used as second or third line therapy for the treatment of acute myeloid leukaemia (AML) in patients who have relapsed or are refractory following initial therapy. If licensed, it would offer an additional treatment option for these patients. Elacytarabine is an elaidic acid ester of ara-C (cytarabine) that enters the cell through the plasma membrane by passive diffusion. Its cytotoxic activity is thought to be mediated through increased cellular uptake, decreased deactivation and prolonged exposure to the active metabolite ara-C triphosphate (ara-CTP) within the cell. It is not currently licensed for any other indication.

The UK incidence of AML in adults is 10 per 100,000 population, with around 2,200 adults diagnosed every year. Complete remission is achieved in 50% to 80% of adult patients with AML, but only 20% to 30% of cases experience long-term disease-free survival and a potential cure. In England and Wales, there were 2,493 deaths from AML registered in 2010. In 2010-2011 there were 31,719 admissions for AML in England, resulting in 120,390 bed days, which includes 33,928 finished consultant episodes.

Relapse occurs in over 50% of patients and treatment options for these patients remain limited and include: high dose cytarabine, combination chemotherapy regimens, best supportive and palliative care. Elacytarabine is currently in one phase III clinical trial comparing its effect on overall survival against treatment with investigators choice of chemotherapy regimens. This trial is expected to complete in March 2013.
TARGET GROUP

- Acute myeloid leukaemia (AML); relapsed or refractory – second or third line.

TECHNOLOGY

DESCRIPTION

Elacytarabine (CP-4055) is an elaidic acid ester of ara-C (cytarabine) that enters the cell by passive diffusion through the plasma membrane\(^1\). Cytarabine is hydrophilic and requires facilitated diffusion via nucleotide-specific membrane transporters to enter cells\(^2\). The human equilibrative nucleoside transporter (hENT1) is responsible for most of cytarabine’s influx into human leukaemic blast cells\(^2\). Unlike cytarabine, elacytarabine enters cells independently of nucleotide transporters (such as the hENT1)\(^3\), and as a result, it is taken up by cancer cells that are resistant to cytarabine due to deficient expression of hENT1. The enhanced cytotoxic activity of elacytarabine is thought to be mediated through increased cellular uptake, decreased deactivation and prolonged exposure to the active metabolite ara-C triphosphate (ara-CTP) within the cell\(^1\). In clinical trials elacytarabine is administered intravenously (IV) at 2,000mg/m\(^2\) daily on days 1-5 of a 21 day cycle.

INNOVATION and/or ADVANTAGES

If licensed, elacytarabine may offer an additional treatment option in patients with AML who have relapsed or are refractory following initial therapy.

DEVELOPER

Clavis Pharma.

PATIENT GROUP

BACKGROUND

AML is a malignant disease of the bone marrow in which hematopoietic precursors are arrested in an early stage of development. Most AML subtypes are distinguished from other related blood disorders by the presence of more than 20% blasts in the bone marrow\(^4\). Several factors have been implicated in the causation of AML, including antecedent hematologic disorders, familial syndromes, environmental exposures, and drug exposures. However, most patients who present with de novo AML have no identifiable risk factor\(^4\). Patients with AML present with symptoms resulting from bone marrow failure, symptoms resulting from organ infiltration with leukemic cells, or both\(^5\).

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to Improving Outcomes: A Strategy for Cancer (2011).
**CLINICAL NEED and BURDEN OF DISEASE**

Haematological cancers together represent the fifth most common type of cancer in the UK, accounting for 7% of all cancers\(^6\). The UK incidence of AML in adults is 10 per 100,000 population, with around 2,200 adults diagnosed every year\(^7\). AML affects all ages, however its incidence increases with age, with a median age of onset of 70, and two thirds of all cases diagnosed in the UK are in those aged over 60 years\(^8\). The incidence is slightly higher in males than in females\(^8\). Complete remission is achieved in 50% to 80% of adult patients with AML, but only 20% to 30% of cases experience long-term disease-free survival and a potential cure\(^10\). The majority of adults diagnosed with AML are destined to relapse and since therapeutic options remain limited, disease recurrence represents the major cause of treatment failure\(^11\).

In England and Wales, there were 2,493 deaths from AML registered in 2010 of which 2,145 were in those aged 60 years old or over\(^12\). In 2010-2011 there were 31,719 admissions for AML in England, resulting in 120,390 bed days, and 33,928 finished consultant episodes\(^13\) (ICD10 C92.0).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Decitabine for the treatment of newly diagnosed acute myeloid leukaemia for whom intensive chemotherapy is considered inappropriate. Expected date of issue to be confirmed\(^14\).
- NICE technology appraisal. Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia. 2011\(^15\).
- NICE cancer service guideline. Haemato-oncology. 2003\(^6\).

**Other Guidance**

- European Society for Medical Oncology (ESMO). Acute myeloblastic leukemia in adult patients: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. 2009\(^18\).

**EXISTING COMPARATORS and TREATMENTS**

Relapse occurs in over 50% of patients and treatment options for these patients remain limited. Current treatment options for refractory/relapsed AML include:

- High dose cytarabine – pyrimidine antagonist.
- Daunorubicin – anthracycline antibiotic.
- Combination chemotherapy regimens:
  - MEC (mitomycin, etoposide and cytarabine)\(^18\)
  - CLAG-M (cladribine, cytarabine, mitoxantrone, and filgrastim)\(^19\)
  - FLAG-IDA (fludarabine, cytarabine, idarubicin, and filgrastim)\(^20\)
ADE (cytarabine, daunorubicin and etoposide)\(^a\)

- Haematopoietic stem cell transplantation – not recommended for older patients or those with significant co morbidities\(^21\).
- Best supportive care.
- Palliative care.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
<th>Schedule</th>
<th>Follow-up</th>
<th>Primary outcome/s</th>
<th>Secondary outcome/s</th>
<th>Key results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLAVELA, NCT01147939, CP4055-306, 2009-014445-80; elacytarabine vs investigators choice; phase III.</td>
<td>Clavis Pharma.</td>
<td>Ongoing.</td>
<td>Trial registry(^{23}) and abstract(^{24}).</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
<td>Randomised, active-controlled.</td>
<td>n=380 (planned); adults; relapsed/refractory AML; failed to respond to 2 or 3 different AML treatments</td>
<td>Randomised to elacytarabine IV 2,000mg/m(^2) on days 1-5 of a 21 day cycle for 1-2 cycles followed by consolidation therapy, vs investigators choice(^5).</td>
<td>Event driven study; primary analyses at 300 events then follow-up surviving patients until death.</td>
<td>Overall survival (OS).</td>
<td>Response rate (RR), adverse affects (AEs).</td>
<td>CR, n=5 (8%); CRi, n=6 (10%); median time from start of treatment to remission, 48 days (range 26-69 days).</td>
</tr>
<tr>
<td>NCT00405743, CP4055-106, 2006-000868-83; elacytarabine; phase II.</td>
<td>Clavis Pharma.</td>
<td>Complete and published in abstract(^22).</td>
<td>Trial registry(^{29}) and abstract(^{22}).</td>
<td>EU (inc UK) and USA.</td>
<td>Non-randomised.</td>
<td>n=61; adults; AML; failed previous induction therapy.</td>
<td>Patients receive elacytarabine 2,000mg/m(^2) IV on day 1-5 of a 21 day cycle for an average of 1.5 cycles.</td>
<td>Active treatment period 1-2 months then 6 months follow-up.</td>
<td>OS, CR.</td>
<td>AEs.</td>
<td>DFS, event free survival (EFS).</td>
</tr>
<tr>
<td>NCT01035502, CP4055-205, 2008-008518-38; elacytarabine plus idarubicin; phase II.</td>
<td>Clavis Pharma.</td>
<td>Ongoing.</td>
<td>Trial registry(^{26}), abstract(^{27}), poster(^{28}).</td>
<td>EU and USA.</td>
<td>Non-randomised.</td>
<td>n=50 (planned); adults; AML; failed first remission-induction course of a cytarabine based regimen.</td>
<td>Patients receive elacytarabine 1,000mg/m(^2) IV on day 1-5 of a 21 day cycle for 2 cycles, plus idarubicin 12mg/m(^2) IV on day 1-3 of a 21 day cycle, followed by consolidation therapy.</td>
<td>Active treatment period 3-6 months then 6-9 months follow-up.</td>
<td>Rate of complete remission (CR(^5)).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Expert opinion.

\(^{b}\) Choice of cytarabine (high dose); mitoxantrone, etoposide and cytarabine (MEC); fludarabine, cytarabine, G-CSF ± idarubicin (FLAG/FLAG-IDA); low dose cytarabine, azacitadine or decitabine; hydroxyurea; or supportive care only.

\(^{c}\) CR defined as: ≤5% blasts, neutrophil count ≥1x10\(^9\)/L, platelet count ≥100x10\(^9\)/L.
28-114); median duration of remission 95 days (range 4-230); median OS, 5.3 months; 6-month survival, 43%.

(8%); median time from start of treatment to remission, 40 days (25-60); referred for stem cell transplantation, n=9 (35%); 30 day all cause mortality, 11%.

Adverse effects (AEs)

- Common AEs include thrombocytopenia, leukopenia, febrile neutropenia, lymphopenia, fatigue and pyrexia.

- Common AEs include leukopenia, febrile neutropenia, infections/sepsis, thrombocytopenia.

**Expected reporting date**

- Estimated study completion date March 2013.

- Study completion date May 2010.

- Estimated study completion date Oct 2013.

#### ESTIMATED COST and IMPACT

**COST**

The cost of elacytarabine is yet to be determinedd. The cost of other selected treatments for AML are29:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytarabine</td>
<td>1g/m² IV (once or twice daily)</td>
<td>£335 per 5-day treatment course</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>45mg/m² IV (once daily)</td>
<td>£660 per 3-day treatment course</td>
</tr>
<tr>
<td>Azacitidine</td>
<td>75 mg/m² IV or subcutaneous (once daily)</td>
<td>£3370 per 7-day treatment course</td>
</tr>
</tbody>
</table>

**IMPACT - SPECULATIVE**

<table>
<thead>
<tr>
<th>Impact on Patients and Carers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ Reduced mortality/increased length of survival</td>
<td>☑ Reduced symptoms or disability</td>
</tr>
<tr>
<td>☐ Other</td>
<td>☐ No impact identified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Impact on Services</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Increased use of existing services</td>
<td>☐ Decreased use of existing services</td>
</tr>
<tr>
<td>☐ Re-organisation of existing services</td>
<td>☐ Need for new services</td>
</tr>
<tr>
<td>☐ Other</td>
<td>☑ None identified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Impact on Costs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Increased drug treatment costs</td>
<td>☐ Reduced drug treatment costs</td>
</tr>
<tr>
<td>☐ Other increase in costs</td>
<td>☐ Other reduction in costs</td>
</tr>
<tr>
<td>☑ Other: uncertain unit cost compared to alternative treatments</td>
<td>☐ None identified</td>
</tr>
</tbody>
</table>

---

d Based on average bodyweight 76.9kg and average surface area 1.7m².
Other Issues

- Clinical uncertainty or other research question

REFERENCES


