National Horizon Scanning Centre

Arsenic trioxide (Trisenox) for acute promyelocytic leukaemia - first line therapy

December 2007

This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.
Arsenic trioxide (Trisenox) for acute promyelocytic leukaemia - first line therapy

Target group
- Acute promyelocytic leukaemia (APL) - first line consolidation therapy for adults

Background
Acute myeloid leukaemia (AML) is a form of bone marrow cancer where the malignant transformation and uncontrolled proliferation of an abnormally differentiated, long-lived myeloid progenitor cell results in high circulating numbers of immature blood forms and replacement of normal marrow by malignant cells.

APL is a subcategory of AML and in 95% of cases of APL, the retinoic acid receptor alpha (RARα) gene on chromosome 17 is involved in a reciprocal translocation with the promyelocytic leukemia gene (PML) on chromosome 15. The resultant fusion protein (PML/RARα oncoprotein) disrupts the function of RARα, blocking the normal maturation of myeloid precursors to granulocytes. APL is unique from other forms of AML in its responsiveness to all trans retinoic acid (ATRA, tretinoin) therapy.

Technology description
Arsenic trioxide (As$_2$O$_3$) is a form of naturally occurring arsenic, and is believed to have multiple mechanisms of action, including apoptosis induction by damaging or degradation of the fusion protein PML/RARα. It is anticipated that arsenic trioxide consolidation therapy will be used in addition to the standard therapy, with a view to improving duration of response and survival. Arsenic trioxide is given as an intravenous (iv) infusion at 10 mg per day over a period of 1 to 4 hours and is administered for 2 to 5 days a week for a varying length of time (sometimes with time off between cycles). Arsenic trioxide may be given in combination with dexamethasone and/or ascorbic acid.

Arsenic trioxide is already licensed for the treatment of patients with APL who are refractory to or have relapsed from previous treatment with retinoid and anthracycline chemotherapy.

The major side effects associated with arsenic trioxide include: leucocyte activation syndrome, hyperglycaemia, hypokalaemia, leucocytosis, QT interval prolongation, atrial fibrillation, haemorrhage, dyspnoea, pleuritic pain, musculoskeletal pain, paraesthesia and fatigue.

Innovation and/or advantages
It is anticipated that arsenic trioxide consolidation therapy will be used in addition to the standard therapy, with a view to improving duration of response and survival.

Developer
Cephalon
Place of use

- Home care e.g. home dialysis
- Community or residential care e.g. district nurses, physio
- Secondary care e.g. general, non-specialist hospital
- Primary care e.g. used by GPs or practice nurses
- General public e.g. over the counter
- Emergency care e.g. paramedic services, trauma care
- Tertiary care e.g. highly specialist services or hospital
- Other:

Availability, launch or marketing dates, and licensing plans:
In phase III clinical trials.

NHS or Government priority area:
This topic is relevant to the NHS Cancer Plan

Relevant guidance
- NICE: Improving outcomes in haemato-oncology cancer.
- Department of Health: Specialised Services National Definition Set: 2 specialised services for blood and marrow transplantation (all ages).

Clinical need and burden of disease
There were 1,878 new cases of AM L in England and Wales in 2002 and 1,776 deaths in 2003. 1 in 10 cases of adult AML are APL. APL differs from other subtypes of AML in that patients are on average younger with a median age of 40 years.

Existing comparators and treatments
Current first line treatment of APL includes:
- Tretinoin (ATRA) which can lead to a cure in more than 70% of patients, followed by:
- Anthracycline-based cytotoxic chemotherapy, with
- Mercaptopurine and methotrexate (used more in context of maintenance/consolidation therapy)

Aggressive supportive care includes the management of disseminated intravascular coagulation (DIC).

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial name or code</th>
<th>Intergroup 9710; previously untreated APL; phase III</th>
<th>NCT00517712; newly diagnosed APL; phase III</th>
<th>NCT00378365; previously untreated APL; phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>NCI and Cancer and Leukemia Group B (CALGB) under agreement with Cephalon.</td>
<td>Christian Medical College, Ministry of Science and Technology, India.</td>
<td>Assistance Publique – Hopitaux de Paris, France.</td>
</tr>
<tr>
<td>Status</td>
<td>Published</td>
<td>Ongoing - still recruiting</td>
<td>Ongoing - still recruiting</td>
</tr>
<tr>
<td>Location</td>
<td>USA</td>
<td>India</td>
<td>France</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised</td>
<td>Randomised, active control, open-label</td>
<td>Randomised, active control, open-label</td>
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</tbody>
</table>
| Participants      | n=582; newly diagnosed APL; randomised to: Arm 1. ATRA, daunorubicin, and cytarabine; followed by two post-remission courses of | n=400; adults; newly diagnosed APL; active disease. Randomised to single agent arsenic trioxide | n=800  
|                   | o Patients ≤70 years with WBC <10,000/mm³ receive either: i) induction with ATRA and | | |

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News on emerging technologies in healthcare
ATRA plus daunorubicin. Arm 2. As arm 1 but with two 25-day courses of iv arsenic trioxide with ATRA and chemotherapy, given immediately after complete remission (CR) or partial remission (PR) and before standard post-remission regimen. Patients who remained free of leukaemia received an additional year of oral chemotherapy. Patients <15 years of age (11% of the group) were not assigned to arsenic trioxide.

maintenance therapy for 6 months or 12 months. anthracycline-AraC, followed by 2 consolidation courses and maintenance with chemotherapy and ATRA, or

ii) the same regimen but with arsenic trioxide or ATRA instead of AraC during consolidation courses.

- Patients ≤ 70 years with WBC>10,000/mm³ - daunorubicin with or without arsenic trioxide in the 2 consolidation cycles.

- Patients >70 years with WBC<10,000/mm³ - reduced dose of chemotherapy with arsenic trioxide during consolidation courses and the 1st year of maintenance.

- Patients >70 years with WBC>10,000/mm³ - same as those with low WBC but with moderate doses of chemotherapy during induction and the first consolidation course.

Follow-up

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Median follow-up 29 months.</th>
<th>6 or 12 months</th>
<th>Minimum 2 years</th>
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<tbody>
<tr>
<td>Primary outcome</td>
<td>Safety and efficacy.</td>
<td>Haematological remission at 60 days; molecular remission at 3 months; duration of response</td>
<td>Event free survival (EFS) at 2 years from CR or diagnosis; relapse (molecular or haematological)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Overall survival (OS); CR; PR.</td>
<td>Toxicity, relapse, treatment related mortality</td>
<td>Survival at 2 years; treatment related mortality and morbidity</td>
</tr>
<tr>
<td>Key results</td>
<td>77% on arsenic vs 59% on standard therapy remained alive and in remission. 86% on arsenic vs 77% on standard therapy survived to 3 years.</td>
<td>Study start: June 2004. Expected completion: July 2009</td>
<td>Study start: October 2006. Expected completion: September 2013</td>
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<td>Adverse effects</td>
<td>Slightly higher incidence of headache and infection with arsenic.</td>
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</table>

Estimated cost and cost impact

The cost of 2 x 25-day courses of arsenic trioxide at 10 mg per day for an average adult is £12,545.

Potential or intended impact – speculative

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Patients
☑ Reduced morbidity  ☑ Reduced mortality or increased survival  ☑ Improved quality of life for patients and/or carers
☐ Quicker, earlier or more accurate diagnosis or identification of disease  ☐ Other:
☐ Non identified

Services
☑ Increased use e.g. length of stay, out-patient visits  ☐ Service reorganisation required  ☐ Staff or training required
☐ Decreased use  ☐ Other:
☐ Non identified

Costs
☐ Increased unit cost compared to alternative  ☐ Increased costs: more patients coming for treatment  ☐ Increased costs: capital investment needed
☑ New costs:
☐ Savings:
☐ Other:

References

2 Department of Health: Specialised Services National Definition Set: 2 specialised services for blood and marrow transplantation (all ages). February 2007.
3 CancerStats, Cancer Research UK 2006
4 CancerStats, Cancer Research UK 2005