Technology Brief

Theralite™ for treatment of renal failure in patients with multiple myeloma

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This brief was prepared by Dr Vicki Foerster and Dr Prema Thavaneswaran for ASERNIP-S.
NAME OF TECHNOLOGY

Theralite™ for treatment of renal failure in patients with multiple myeloma

PURPOSE AND TARGET GROUP

To remove serum free light chains in adult patients in renal failure due to multiple myeloma, thus aiming for dialysis independence and reduced morbidity and mortality

STAGE OF DEVELOPMENT IN AUSTRALIA

☐ Yet to emerge
☐ Experimental
☒ Investigational
☐ Nearly established

☒ Established
☐ Established but changed indication or modification of technique
☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☒ Yes
☐ No
☐ Not applicable

ARTG number: 146423

INTERNATIONAL UTILISATION

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused</th>
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<tbody>
<tr>
<td>Australia</td>
<td>☑</td>
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<tr>
<td>Canada</td>
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<td>☑ (assumed; regulatory approval granted)</td>
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<td>Europe¹</td>
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<td>United Kingdom</td>
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IMPACT SUMMARY

Gambro AB (Lund, Sweden) provides the Theralite™ High Cut-Off haemodialysis (HCO-HD) device with the aim of filtering free light chains (FLCs) from the serum of patients with multiple myeloma (MM) who are in severe renal failure. The technology would be made available through hospitals and dialysis centres as an alternative to traditional haemodialysis (HD) dialysers which have been found to be minimally effective.
Annually, about 1300 new cases of MM are diagnosed in Australia, and at least 10 percent of these patients will experience renal failure severe enough to require long-term HD. A single case series study (n=19) examined the impact of HCO-HD (plus chemotherapy). Thirteen patients (68%) completed the course of therapy and all 13 became dialysis-independent versus six patients who were unable to complete therapy as planned, only one of whom was able to regain renal function. A study update (67 patients, 16 dialysis centres, and 9 countries) reported that 63% of patients treated with HCO-HD became dialysis-independent versus the expected proportion of about 16 percent.

A cost effectiveness analysis (CEA) used a lifetime decision tree model that followed patients from initial presentation for HD to death. A health system perspective was taken. The model predicted an average survival of 34 months for HCO-HD versus 20 months for standard HD; quality-adjusted life years (QALYS) were 22 months for HCO-HD versus 13 months for HD; and the expected costs of treatment were lower for HCO-HD, making it the dominant economic strategy.

**BACKGROUND**

Plasma cells are an important part of the immune system, and produce immunoglobulins that help to fight infections and disease. MM\(^2\) is a progressive cancer of the plasma cells, characterised by excessive numbers of abnormal plasma cells in the bone marrow and overproduction of intact immunoglobulins (IgG, IgA, IgD or IgE) or free light chains (FLCs) (Gambro 2010).

In healthy people, FLCs are rapidly removed from the circulation by renal clearance but in patients with MM, serum concentrations of FLCs may be several thousand times higher than normal. These high concentrations of FLCs cannot be effectively cleared by the kidney. They co-precipitate with local proteins to form waxy casts, block the flow of urine, cause interstitial inflammation, and result in ‘cast nephropathy’ or ‘myeloma kidney’ (Hutchison et al 2009).

Up to 50 per cent of patients with MM have renal impairment at presentation, and 10 to 20 per cent become dependent on dialysis, most requiring dialysis long-term. Unfortunately, traditional HD is minimally effective, as FLCs are too large to move through the pores of standard dialysis membranes. Therefore, the management options for the severe renal failure experienced by 10 to 20 per cent of patients with MM are limited.

Researchers from the University of Birmingham tested seven types of dialysers in vitro and found the Gambro HCO1100 to be superior. Model calculations suggested that the device

\(^1\) According to Grima et al (2011) in a cost-effectiveness analysis, “[This] technology is commercially available and currently used in regular clinical practice in Europe and other parts of the world.”

\(^2\) Common clinical manifestations of MM are hypocalcaemia, anaemia, renal damage, increased susceptibility to bacterial infection, and impaired production of normal immunoglobulins (Gambro 2010).
might remove 90 percent of FLCs over 3-weeks, so the device was then evaluated in eight patients (in combination with chemotherapy); serum FLCs dropped by 35 to 70 per cent within two hours (Hutchison et al 2007).

The Gambro device uses a unique membrane technology to target FLCs and other plasma components with a molecular weight of up to 45 kDa, while ensuring effective retention of larger proteins with molecular weights greater than 60 kDa such as clotting factors and immunoglobulins. The device is used with a HD machine, and one new device per treatment session is required (Gambro 2011).

**CLINICAL NEED AND BURDEN OF DISEASE**

Australian Institute of Health and Welfare (AIHW) data reported 1312 new cases of MM in 2008 (772 men and 540 women) (AIHW 2011). Patient numbers have been steadily increasing as the country’s population grows, although the rate of myeloma as a proportion of all cancers has remained stable at about 1.2 percent. The incidence of the disorder rises with age and in 2008 peak age was 75-79 years in both sexes.

Of patients with newly diagnosed MM, 10 to 20 percent have dialysis-dependent acute renal failure caused by FLCs; of these, 80 to 90 percent require long-term renal replacement therapy. Early treatment using plasma exchange reduces serum FLC concentrations; however, randomised controlled trials (RCTs) have shown no evidence of renal recovery, attributed to low procedure efficiency (Hutchison et al 2007).

Most patients remain on long-term dialysis, with a greatly increased morbidity and mortality compared with patients who remain dialysis-independent (Hutchison et al 2008a).

**DIFFUSION OF TECHNOLOGY**

**Australia**

Theralite has been approved for use in Australia and is listed on the Australian Register of Therapeutic Goods (ARTG number 146423).

Theralite is in limited clinical use in Australia. In Victoria, a two-year study of HCO-HD for the management of acute kidney injury from myeloma cast nephropathy was funded through a Victorian State Government New Technology grant (Ramessur et al 2011). It is likely that this study is part of the larger ‘Chart Audit of Renal Recovery in Multiple Myeloma (CHARMM) Study’ (Hutchison et al 2009b; Bridoux et al 2011, page 27), the results of which are discussed in this brief. Clinical expert opinion suggests that currently, the cost of this technology does preclude it from being widely implemented in many centres in Australia.

**Canada and the United States (USA)**

In Canada, Gambro’s Theralite ‘high cut-off dialyser’ was approved for marketing as a Class III device in November 2009 (Licence #81336) (Health Canada 2011). The device has not received 510(k) approval from the USA Food and Drug Administration (FDA 2011), although the FDA granted a Humanitarian Use Device (HUD) designation to the Theralite membrane
for the treatment of myeloma kidney in patients with MM (Gambro 2010). According to the manufacturer, this is the first step toward obtaining marketing approval in the USA (Gambro 2010).

Europe
Theralite HCO-HD technology has been commercially available since 2007 in Europe, according to the device manufacturer (Gambro 2010). Essentially all patient-related research to date has been conducted in the United Kingdom (UK) and an RCT in several countries including the UK and Germany is currently recruiting patients (planned enrolment is 90). A multicentre French RCT is also currently recruiting patients. According to Grima et al (2011) in a cost-effectiveness analysis, ‘[This] technology is commercially available and currently used in regular clinical practice in Europe and other parts of the world.’ According to the manufacturer, Germany and Austria currently have forms of reimbursement in place for this technology, and in Switzerland a decision regarding full reimbursement is expected to be made shortly.

Comparators
To remove the over-abundance of FLCs from serum, the historical approach has been plasma exchange; however, its efficacy has not been established (Hutchison et al 2008b). FLCs are present in similar concentrations in serum, the extravascular compartment, and tissue oedema fluid, with the intravascular compartment containing only 15 to 20 percent of the total. Plasma exchange therefore has minimal impact (Hutchison et al 2007). In addition, standard dialysers are also ineffective when used to remove FLCs because their pores are too small to allow FLCs to pass through (Hutchison et al 2007; Gambro 2009).

Safety and Effectiveness Issues
Study description
Only one small study was located (Hutchison et al 2009a), with patient overlap occurring with previous studies by the same authors (Hutchison et al 2007, Hutchison et al 2008a). This single-centre, prospective, case series pilot study (level IV intervention evidence) was undertaken between April 2006 and May 2008 in Birmingham, UK. The objectives of the study were: (a) to determine whether chemotherapy in combination with FLC removal by HCO-HD resulted in sustained reductions in serum FLC concentrations, and (b) to relate changes in serum FLC levels to renal recovery.

Included in this study were 19 patients with MM and dialysis-dependent renal failure (eGFR <15 ml/min/1.73 m²) who demonstrated cast nephropathy on renal biopsy. Mean patient age was 60 years (range 38-81 years) and 74 per cent of patients were male. Treatment combined standard chemotherapy plus FLC removal using two Gambro HCO 1100 dialysers in series (Table 1). The dialysis schedule started intensively, tapered to six hours 3 times a week, and continued until the patient was independent of dialysis.
Table 1  Overview of Hutchison et al (2009a enrolment)

<table>
<thead>
<tr>
<th>Study Type &amp; Level of Evidence (See Appendix)</th>
<th>Patient Enrolment</th>
<th>Exclusion Criteria</th>
<th>Treatment Protocol</th>
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<tbody>
<tr>
<td>Prospective, observational, open label, pilot study, level IV evidence</td>
<td>n=19 adults w/ MM and dialysis-dependent renal failure who demonstrated cast nephropathy on renal biopsy; 16 had de novo MM &amp; 3 had relapsing disease</td>
<td>3 patients of 22 initially assessed were excluded due to relapsing disease not suitable for new therapies (2) and dementia (1)</td>
<td>Standard chemotherapy + HCO-HD:</td>
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<td></td>
<td></td>
<td>• Chemotherapy regimen:</td>
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<tr>
<td></td>
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<td>o De novo MM: high dose dexamethasone + cyclophosphamide, thalidomide &amp; / or vincristine/doxorubicin</td>
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<td>o Relapsing MM: high dose dexamethasone + doxorubicin + bortezomib</td>
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<td></td>
<td>HCO-HD: FLC removal via 2 Gambro HCO1100 dialysers in series; schedule was 8 hours/day x 5 days, 8 hours alternate days x 12 days, then 6 hours 3 times/week, continued until patient was independent of dialysis</td>
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FLC: free light chain; HCO-HD: high cut-off haemodialysis; MM: multiple myeloma

Effectiveness

Thirteen of 19 patients (68%) completed 6-weeks of uninterrupted therapy and all sustained early reductions in FLC concentrations, with a median reduction of 85 per cent (range 50-97%). The remaining six patients (32%) had chemotherapy interrupted, primarily due to infection, and none had sustained FLC reductions. Two of these six patients were able to restart chemotherapy within 6 weeks and two after 6 weeks. The remaining two patients died (one each of fungal pneumonia and intracranial haemorrhage).

All 13 patients with early FLC reduction became independent of dialysis at a median of 24 days (range 8-58 days). Three months after the start of treatment, these 13 patients had a median estimated GFR of 40 ml/min (range 11-83 ml/min). Of the six patients with interrupted courses of chemotherapy, two died of their disease and only one of the remaining four was able to become independent of dialysis (at 105 days).

Kaplan-Meier survival analysis showed that early interruption of chemotherapy was associated with significantly worse outcomes ($P<0.002$). The median survival for these patients was 53 days (range 21-331 days), compared with patients who completed chemotherapy who were alive at a median follow-up of 360 days (range 150-630 days; $P<0.02$).

Safety

The authors reported that HD using the Gambro device was well tolerated by all patients, with no unexpected adverse events (AEs) related to the procedure. Specifically, no non-infective complications related to venous access or anticoagulation were reported. However, infections were not uncommon, with five patients required to interrupt chemotherapy due to line sepsis (3), pneumonia (1) and neutropenic sepsis (1). Another patient was required to interrupt chemotherapy due to dermatitis. Three of the 13 patients who did not require interruption of chemotherapy experienced infections during their treatment course (two urinary tract infections and one line-related infection).
Updated study information
The most recent available data on HCO-HD comes from the ‘Chart Audit of Renal Recovery in Multiple Myeloma (CHAR2M2) Study’ (Hutchison et al 2009b; Bridoux et al 2011, page 27). A 2011 conference abstract and a separate presentation state that, across 16 dialysis centres in Europe and Australia, 63 per cent of 67 patients treated with HCO-HD became dialysis independent after 12 sessions.3 The rate of dialysis independence was higher (64% versus 56%, P=0.04) in the 76% of patients with de novo MM versus the 24% with relapsing MM. Dialysis related AEs were reported in six per cent of patients (no detail was provided).

Cost impact
The cost of each Gambro HCO1100 dialyser in Australia, provided by the Sponsor (Gambro Pty Ltd), is $1,470. One new dialyser is used for each treatment session. Patients undergo a series of treatments, and based on the results from the ‘Chart Audit of Renal Recovery in Multiple Myeloma (CHAR2M2) Study’, approximately 12 sessions are required in order for patients to become dialysis independent. As mentioned earlier, clinical expert opinion suggests that currently, the cost of this technology does preclude it from being widely implemented in many centres in Australia; however, it is important to balance this with the long-term cost of HD, as well as the lack of available management options for MM patients with severe renal failure.

A manufacturer-funded4 CEA compared HCO-HD to standard HD in the management of myeloma kidney (Grima et al 2011).5 The CEA used a lifetime decision tree model that followed patients from treatment of the initial presentation for HD to death. Clinical data came from Hutchinson et al publications and expert opinion, costs were based on those in the UK, and a UK National Health Service perspective was employed (i.e. this study only considered costs directly borne by the health service). Costs and outcomes beyond the first year were discounted at a rate of 3.5 per cent.

Grima’s model predicted an average survival of about 34 months for patients in the HCO-HD group versus 20 months for patients on standard HD. QALY calculation was about 22 months for HCO-HD versus 13 months for HD. Expected costs of treatment were lower for HCO-HD at about £25,000 versus £31,000 per patient for HD (due to avoidance of long-term HD in the former group).

Cost-effectiveness ratios were not calculated as HCO-HD was more effective and less costly, i.e. dominant over standard HD. Sensitivity analysis showed that HCO-HD remained the dominant strategy (lower cost and greater QALYs) in all sensitivity analyses except when the

3 In contrast, renal recovery in patients on haemodialysis ranges from 4% to 24% (mean across studies 16%) (Grima et al 2011).
4 The authors had independent control over model structure, data inputs, interpretation, and manuscript development; however, the manufacturer provided comment on the analysis and manuscript.
5 The key clinical expert in this area (C. A. Hutchinson) was also an author.
percentage of patients who recovered after standard HD increased from the base case of 16 per cent\(^3\) to 37 per cent.

The authors concluded that ‘Overall, the analysis found that treatment of myeloma kidney using an extended schedule of HCO-HD may substantially improve renal recovery ... compared to standard HD, resulting in greater life expectancy and cost savings due to avoided chronic dialysis. The limitations of the study include those common to rare diseases including small study sizes and limited natural history data’.

Informal advice from Australian nephrologists indicates that dialyser costs are likely to reduce as competitors enter the market over the next few years.

**ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**
No issues were identified from the retrieved material.

**OTHER ISSUES**

**Upcoming clinical trials**
The ‘European Trial of Free Light Chain Removal by Extended Haemodialysis in Cast Nephropathy (EuLITE)’ (NCT00700531) is a trial that will be led by the University Hospital, Birmingham, United Kingdom with collaborators, Gambro Renal Products, Inc and Ortho Biotech, Inc. The multi-site (Germany and United Kingdom), parallel assignment, open label, efficacy study is currently recruiting adult participants (n=90) who will be centrally randomised to:
- Trial chemotherapy (bortezomib, doxorubicin and dexamethasone) and FLC removal haemodialysis (two Gambro HCO1100 dialysers in series over an intensive treatment schedule); OR
- Trial chemotherapy and standard high flux haemodialysis.

The primary outcome is independence from dialysis at 3 months. Secondary outcomes include duration of dialysis, serum FLC concentrations, myeloma response, and survival. A study protocol has been published (Hutchinson et al 2008b; ClinicalTrials.gov 2010).

In addition, there is another RCT that is currently ongoing across 50 centres in France, which is being sponsored by the French government. This RCT, known as MYRE or PHRC, has the same aims as the EuLITE study.

**Conflict of interest of study authors**
Until recently, only one research team has been involved in studies of this technology, i.e. Hutchinson et al from the University of Birmingham in the UK, and research has been funded by the device manufacturer. The lead author and several colleagues have close relationships (employees or directors) with The Binding Site Ltd in Birmingham, a company developing immunodiagnostic assays, including those to detect FLCs in patients with MM.
The Binding Site is providing the immunoassays to measure FLCs free of charge for the planned RCT (Hutchinson et al 2008b).

**SUMMARY OF FINDINGS**
MM is an uncommon cancer (1.2% of all cancers in Australia). Of patients with MM, 10 to 20 percent have severe renal failure requiring dialysis. Traditional HD has provided inadequate treatment, which has necessitated the development of HCO-HD (Theralite) technology. The only study currently available is very small (n=19) and of low rigour (level IV evidence), although its findings were dramatic with respect to renal recovery leading to independence from dialysis and survival. A CEA showed HCO-HD to be the dominant strategy over standard HD (i.e. lower cost and greater QALYs), although clinical data were mainly drawn from small observational studies performed by the same research team.

**HEALTHPACT ASSESSMENT:**
Based on limited clinical data, HCO-HD appears to be a safe and effective treatment for selected patients with MM and severe renal failure who currently have few treatment options. Two multi-centre RCTs are currently recruiting patients, and the results from these trials will provide valuable information about the utility of HCO-HD for patients with MM and severe renal failure. Therefore, HealthPACT wish to monitor the technology, which will be reviewed in 12 months time.

**NUMBER OF STUDIES INCLUDED**
All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the following link on the HealthPACT web site.

| Total number of studies | 1 |
| Total number of intervention level IV studies | 1 |

**REFERENCES**


**SEARCH CRITERIA TO BE USED**

Theralite OR Free light chain removal OR High cut-off haemodialysis OR HCO-HD; Renal failure OR Cast nephropathy OR Multiple myeloma OR Myeloma kidney