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The production of this *Horizon scanning prioritising summary* was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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PRIORITISING SUMMARY

REGISTER ID: 000285 REFERRAL FROM HEALTHPACT

NAME OF TECHNOLOGY: ELECTROCHEMOTHERAPY (ECT)

PURPOSE AND TARGET GROUP: TREATMENT OF LOCAL MALIGNANT TUMOURS BY ADMINISTRATION OF CHEMOTHERAPY DRUGS FOLLOWED BY ELECTROPORATION

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|---|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input checked="" type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | |
|---|-------------|
| <input type="checkbox"/> Yes | ARTG number |
| <input checked="" type="checkbox"/> No | |
| <input type="checkbox"/> Not applicable | |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Italy		✓	
Spain		✓	
Denmark		✓	
Ireland		✓	

IMPACT SUMMARY:

This prioritising summary examines a method to improve chemotherapy drug delivery for the treatment of cutaneous and subcutaneous tumours, followed by electroporation. The electroporation device, the Medpulsar™ Electroporation Therapy System is currently not approved for use in the United States but has CE mark in Europe (personal communication 6th December 2006). There are ongoing trials of this device being conducted in order to gain FDA approval. This device has been used in Australia for clinical investigation and its results are included in this prioritising summary.

BACKGROUND

Electroporation was first developed in the 1980s as a means to facilitate transport of normally non-permeant¹ molecules into cells. This technique has been used *in vitro* to

¹ Permeant: able to pass through a semi-permeable membrane.

load dyes, DNA, RNA, ions, drugs and proteins into cells while radiotracers, drugs and oligonucleotides have been loaded into cells *in vivo* (Gothelf et al 2006).

Electrochemotherapy (ECT) is a local treatment for metastatic nodules of solid tumours on the skin or subcutaneous tissue, which combines the physical effect of cell membrane poration (electroporation) with simultaneous administration of chemotherapy drugs eg cisplatin and bleomycin. An electric pulse generator applies a rapid series of brief, high-intensity, electrical pulses via a six-needle array electrode into a solid tumour (800-1000 volts/cm for 100 microseconds). This temporarily results in increased cell membrane permeability, enhancing the uptake of non-permeant or poorly permeant chemotherapeutic drugs. After the electric field is discontinued, the pores close within minutes with the drug molecules trapped inside the target cells and without significant damage to the exposed cells (Giardino et al 2006).

ECT is a *palliative* treatment of new tumour nodules but has no effect on the *progression* of disease (Sersa et al 2003).

CLINICAL NEED AND BURDEN OF DISEASE

In Australia there were 8,885 new cases of skin melanoma recorded in the year 2001, a rate of 45.8 per 100,000. In 2001, melanoma was the fourth most common cancer in Australia and accounted for 10% of all new cancer cases (AIHW 2004). It has been estimated that the lifetime risk for developing melanoma is 1 in 25, and 1 in 34 for Australian males and females, respectively (Lens and Dawes 2004)

In 1999, the Caucasian population in the region of Auckland, New Zealand, had the highest incidence of invasive cutaneous malignant melanoma in the world with the age-standardised annual rate of 56 per 100,000 (Lens and Dawes 2004). The cumulative risk of developing melanoma over a lifetime in New Zealand has been reported to be 6 per cent.

DIFFUSION

Electrochemotherapy is currently not used in clinical practice in Australia. However, it is on the verge of becoming standard treatment in palliative treatment of cutaneous and subcutaneous tumour nodules of different malignancies (Sersa et al 2006). An electroporation manufacturer representative confirmed that clinical experience to date in Australia has been in the treatment of melanomas only. The greatest clinical experience with this technique has been in Western Europe (personal communication, 6th December).

COMPARATORS

The gold standard for treatment of primary melanoma is surgical excision. Other treatment options for metastatic lesions vary according to nature of lesion and include radiotherapy, cryotherapy, laser ablation and radiofrequency ablation (Byrne and Thompson 2006).

EFFECTIVENESS AND SAFETY ISSUES

At the time of preparing this prioritising summary there are no studies available comparing ECT to surgical excision. Only studies comparing drug delivery utilising ECT to either intravenous or intra-tumour drug delivery alone were found.

A study (level II intervention evidence) conducted at the Sydney and Newcastle Melanoma Units compared the effect of electroporation after intratumoral injection of bleomycin to the effect of intratumoral bleomycin alone in 19 patients with cutaneous and subcutaneous metastatic melanoma deposits (Byrne et al 2005). This study evaluated lesion response, local complications, time to healing of treated lesions, duration of response and long-term outcome. Response rates were categorised as “complete” if there was no residual disease detected, “partial” if there was a greater than 50% reduction in lesion size, “disease progression” if there was a greater than 25% increase in lesion size and “no change” if lesion did not fall into any of the criteria.

Tumours <0.5ml in volume were injected with 0.5U of bleomycin while all other tumours were injected with 1U of bleomycin per millilitre of tumour volume. The lesions ranged in size from 3mm² to 50mm². Two to 20 minutes after drug injection, electroporation was applied directly into the lesions with an electric pulse generator to a depth slightly greater than the tumour depth.

A total of 46 lesions were treated in this study, however only 36² lesions were available for follow-up at 12-weeks. Thirty-six lesions were randomised to receive either the drug alone (n=19) or the drug followed by electroporation (n=17). In addition, each patient had at least one lesion that served as an internal control. The response rate achieved in the EPT treated group (77%) was significantly greater ($\chi^2 = 9.39$, 1 df, $p = 0.002$) than the response rate in the group treated with bleomycin alone (31%) (Table 1).

² Four patients (10 lesions) did not complete follow-up to 12 weeks. Two patients died from advanced melanoma, one patient transferred hospitals for palliative care and another patient requested excision of all lesions at week 4.

Table 1 Response rates

	Complete Response	Partial Response	No change	Disease progression
Bleomycin alone N = 19	5 (26%)	1 (5%)	3 (15%)	10 (53%)
Bleomycin + EPT N = 18*	13 (72%)	1 (5%)	3 (18%)	1 (5%)

*1 lesion with disease progression was crossed over to intervention group and showed a complete response.

A European project (ESOPE³) was conducted with the aim of preparing standard operating procedures for electrochemotherapy based on the experience of various European studies (Marty et al 2006). This multicentre study (level IV Intervention) evaluated the effect of electroporation combined with either bleomycin or cisplatin administration in 41 patients with different cutaneous and subcutaneous malignancies, including melanoma. Response definitions were as follows: complete response = tumour nodule not palpable; partial response = >50% decrease in tumour size; no change = a <50% reduction and progression of disease was defined by an increase of more than 25% in tumour size.

Bleomycin was administered either intravenously or intra-tumourally at a dose dependent on tumour size and cisplatin intra-tumourally only. The follow-up regime included fortnightly visits in the first month and monthly visits for a maximum of 2-years. Patients experienced a response rate of 85% (74% complete response rate) regardless of tumour histology, type of drug administered or route of administration. At 150 days after treatment (median follow-up 133 days, range 60–380 days) local tumour control rate for electrochemotherapy was 88% with bleomycin given intravenously, 73% with bleomycin given intra-tumourally and 75% with cisplatin given intra-tumourally.

Gothelf et al (2003) summarised the results of 11 clinical trials (level IV intervention evidence) of electrochemotherapy in 96 patients with 411 tumours. Included studies used different methods of drug administration, different electrical fields and electrodes. Response rates for bleomycin ranged from 9 to 57 per cent when delivered intravenously and 6 to 47 per cent for intra-tumoural administration.

COST IMPACT

The cost impact of ECT for the treatment of cancer is currently unknown although study authors claim that it would be a cost-effective treatment compared to surgery and the additional cost of radiation technologies. ECT can be applied in an outpatient regimen which may also provide economic benefits over conventional surgical and or radiation procedures through reduced operating theatre costs, hospital stays and post treatment interventions.

³ European Standard Operating Procedures of Electrochemotherapy

A company representative advised that the purchase cost of electroporation devices is similar to radiofrequency technologies (personal email communication, 6th December 2006).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES The Byrne et al 2005 trial used an electroporation device, the MedPulser[™] Electroporation Therapy System manufactured by Inovio Biomedical Corporation. The manufacturer has conducted several clinical trials (unpublished) of electroporation therapy in the treatment of solid tumours including, head & neck cancer, melanoma, basal cell carcinoma, liver and pancreatic cancer. The MedPulser[™] Electroporation therapy System is being used for Phase III and IV clinical trials for the treatment of newly diagnosed head and neck cancers (ClinicalTrials.gov and Inovio 2006). These studies will include an economic analysis of ECT including hospital costs, extent of medical interventions and medication use.

The Marty et al 2006 study used a different device, the Cliniporator[™] manufactured by IGEA.

CONCLUSION:

Although the use of electroporation for cancer therapy in clinical practice is not an established procedure in Australia its application is continuing to be examined. The potential for the enhancement of drug delivery and therapeutic benefit is being investigated for a wide range of cancers.

HEALTHPACT ACTION:

It is unlikely that this technology would widely diffuse within Australia for the treatment of subcutaneous metastases, which are currently successfully treated by radiotherapists. Therefore HealthPACT has recommended that further assessment of this technology is no longer warranted.

SOURCES OF FURTHER INFORMATION:

AIHW (2004). 'Cancer in Australia 2001' AIHW. [Internet] Available from: <http://www.aihw.gov.au/publications/index.cfm/title/10083> [Accessed 6th December 2006].

Byrne, C. M. & Thompson, J. F. (2006). 'Role of electrochemotherapy in the treatment of metastatic melanoma and other metastatic and primary skin tumors', *Expert Rev Anticancer Ther*, 6 (5), 671-678.

Byrne, C. M., Thompson, J. F. et al (2005). 'Treatment of metastatic melanoma using electroporation therapy with bleomycin (electrochemotherapy)', *Melanoma Res*, 15 (1), 45-51.

ClinicalTrials.gov (2006). *Study using the Medpulser Electroporation System with Bleomycin to treat had and neck cancer*. [Internet]. ClinicalTrials.gov. Available from: <http://www.clinicaltrials.gov/ct/gui/show/NCT00198263> [Accessed 6th December 2006].

Giardino, R., Fini, M. et al (2006). 'Electrochemotherapy a novel approach to the treatment of metastatic nodules on the skin and subcutaneous tissues', *Biomed Pharmacother*, 60 (8), 458-462.

Gothelf, A., Mir, L. M. & Gehl, J. (2003). 'Electrochemotherapy: results of cancer treatment using enhanced delivery of bleomycin by electroporation', *Cancer Treat Rev*, 29 (5), 371-387.

Inovio (2006). *Electroporation Science* [Internet]. Inovio. Available from: <http://www.inovio.com/technology/electroporation.htm> [Accessed 6th December 2006].

Lens, M. B. & Dawes, M. (2004). 'Global perspectives of contemporary epidemiological trends of cutaneous malignant melanoma', *Br J Dermatol*, 150 (2), 179-185.

Marty, M., Sersa, G. et al (2006). 'Electrochemotherapy – An easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: Results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study', *Eur. J. Cancer Suppl*, 4: 3-13.

Mir, L. M., Morsli, N. et al (2003). 'Electrochemotherapy: a new treatment of solid tumors', *J Exp Clin Cancer Res*, 22 (4 Suppl), 145-148.

Sersa, G., Cemazar, M. et al (2006). 'Electrochemotherapy of tumours', *Radiol Oncol*, 40(3), 163-174.

Soden, D. M., Larkin, J. O. et al (2006). 'Successful application of targeted electrochemotherapy using novel flexible electrodes and low dose bleomycin to solid tumours', *Cancer Lett*, 232 (2), 300-310.

LIST OF STUDIES INCLUDED

Total number of studies

Level II Intervention 1

Level IV Intervention 2

SEARCH CRITERIA TO BE USED:

Bleomycin/ therapeutic use

Cell Line, Tumor

Combined Modality Therapy

Electroporation/ methods