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Prioritising Summary Update

Electrochemotherapy for the treatment of local malignant tumours

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UPDATE PRIORITISING SUMMARY 2008

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**

2008 EFFECTIVENESS AND SAFETY ISSUES

Since the initial prioritising summary, there has been one randomised controlled trial, two case series studies, and two case reports published investigating the effectiveness and safety of electrochemotherapy (ECT) for the treatment of cutaneous and subcutaneous malignant tumours.

Gaudy et al (2006) conducted a randomised controlled trial with the purpose of comparing the local control of skin melanoma metastases using bleomycin with ECT and bleomycin alone, and evaluating patient tolerance of the two treatments. Patients recruited in this trial were those with at least two measurable previously untreated skin metastases of melanoma, either in stage III with in-transit metastases or in stage IV with no clear-cut efficacy of systemic chemotherapy on these metastases. Melanoma skin metastases were randomised to be treated in a single process either by intralesional injections of bleomycin alone or by intralesional injections of bleomycin using MedPulser® Electroporation Therapy System. Post-treatment local response was defined in accordance with World Health Organization (WHO) guidelines: complete regression (CR) for total clinical disappearance of tumours; partial response (PR) for a decrease of >50 per cent in tumour size; no change (NC) for an increase of <25 per cent or a decrease of <50 per cent in tumour size; progressive disease (PD) for an increase of >25 per cent in tumour size (WHO 1997).

A total of 54 melanoma skin metastases were treated in 12 patients (four in stage III and eight in stage IV). Among the 54 metastases, 30 were randomised to be treated by bleomycin with ECT with the other 24 lesions treated by bleomycin alone. Only forty metastases in ten patients could be evaluated after treatment as one patient initiated new chemotherapy before study commencement and another one died before the post-treatment evaluation. Among the 40 evaluated metastases, 24 were treated by bleomycin with ECT and 16 by bleomycin alone. In the intention-to-treat population, 11 of the 30 melanoma skin metastases which were treated by bleomycin with ECT demonstrated CR at 12 weeks after the treatment, resulting in a CR rate of 36 per cent. This was significantly greater (p =0.016) than the CR rate of eight per cent (2 in 24 melanoma skin metastases) in the bleomycin alone group. Overall responses[1] were obtained in 46 per cent of metastases (14/30) for bleomycin with ECT group and in 25

[1] Overall response: CR + PR

per cent of metastases (6/24) for bleomycin alone group, with no significant difference between the two groups (p=0.10). In the per protocol population, after at least one month of follow-up, the CR rate was 74 per cent (17/23) in the group of patients treated with bleomycin with ECT, which was significantly higher than the 13 per cent (2/15) in the bleomycin alone group (p =0.017). Bleomycin with ECT had a higher overall tumour response rate than bleomycin alone (87% for bleomycin with ECT vs. 53 % for bleomycin alone); however the study was too small to identify all but a very sizable difference (p=0.35). All of the 12 patients complained of discomfort during the ECT procedure: nine patients (75%) presented with site pain, and three patients (25%) had muscle spasm with myoclonia secondary to electric pulses. No clinical or biologic systemic toxicity was reported in this trial (level II intervention evidence).

Quaglino et al (2008) reported a case series investigating the effectiveness and safety of intravenous injection of bleomycin with ECT for the treatment of cutaneous and/or subcutaneous melanoma metastases. All 14 patients in their studies were in stage III with recurrent or persistent diseases after one or more previous treatments (except bleomycin treatment) of melanoma. The tumour response were categorised according to WHO guidelines as described above. Local tumour control was calculated for each lesion as the time period from response achievement to the demonstration of either recurrence in CR lesions, >25 per cent size increase in PR metastases, or last follow-up date. Time to treatment failure was the time elapsed from the first day of treatment to either therapy discontinuation for any reason, disease relapse which required an alternative treatment, death from any cause, or last follow-up date.

At eight weeks post-treatment, a response was obtained in 13 of all 14 patients (93%), with CRs in all skin metastases in seven (50%) patients and PRs in six patients. For the 233 metastases which were treated with a single ECT session, 216 lesions (93%) responded to the treatment. The response rate was significantly lower in lesions >1cm^2 than that in lesions ≤1cm^2 (73% vs. 98%, p<0.001). The CR rate for all metastases was 58 per cent, with CR rate higher in lesions ≤1cm^2 than in lesions >1cm^2 (68% vs.22%, p<0.001). None of the CR lesions relapsed within the follow-up period. Twenty-nine metastases from three patients received a second or a third ECT session. A further response was obtained in 21 (72%) re-treated lesions. Nine CRs (31%) were observed, five in lesions >1cm^2. The 2-year local tumour control rate was 74.5 per cent. The median duration of time to treatment failure was 18.3 months (range from more than 5 to more than 28 months). No case of haematologic toxicity was reported in this study. The adverse events of ECT included electrode marks and superficial epidermal erosions (100%), as well as erythema and slight oedema (21.4%) (level IV intervention evidence).

Another case series was conducted by Larkin et al (2007), assessing the clinical value of ECT with intratumoural/intravenous bleomycin for the treatment of recurrent, inoperable, or progressive cutaneous or subcutaneous tumours. A total of 111 nodules

in 30 patients were treated. The post-treatment response was classified according to WHO guidelines. With follow-up ranging from two to 12 months, CRs were obtained in 66 tumours (60%). Another 22 per cent of nodules (24/111) showed PRs to the treatment. None of the tumours progressed during the follow-up period. This study also indicated that ECT was more effective for tumours <3cm in diameter, with an overall response rate and CR rate of 91% and 71%, respectively. No adverse events were reported in this study, except two cases of treatment-related mild pain (level IV intervention evidence).

Snoj et al (2007) reported the case of a patient with unresectable cutaneous melanoma metastases treated by intravenous bleomycin with ECT. After four ECT sessions, good local tumour control was observed in the treated area. Even metastases that were not treated by bleomycin with ECT did not progress during the 9-month follow-up. Another case report indicated that bleomycin with ECT was effective and well tolerated in the treatment of recurrent lesions of Kaposi's sarcoma on the penis (Curatolo et al 2008)

2008 COST IMPACT

Colombo et al (2008) carried out a cost-effectiveness analysis, comparing the costs and benefits among ECT (Cliniporator^{TM}), isolated limb perfusion, radiotherapy, interferon-alpha (TNFα), and hyperthermia associated with radiotherapy and chemotherapy, for the treatment of cutaneous or subcutaneous advanced tumours. The direct health costs of this analysis were attributed a value according to the Italian National Healthcare System. This analysis demonstrated that ECT was cost-effective with an incremental cost effectiveness ratio (ICER) of €1,572 to achieve a further additional response. Although isolated limb perfusion was the most effective among all treatment modalities, it is very costly (€18,530) due to the use of expensive TNFα. Isolated limb perfusion had an ICER as high as €92,717. Compared to ECT, treatment using hyperthermia associated with radiotherapy and chemotherapy was more costly and less effective. Other stand-alone therapies, such as radiotherapy and TNFα, were the least effective. The authors concluded that ECT using Cliniporator^{TM} was cost-effective in the treatment of cutaneous or subcutaneous advanced tumours.

2008 SUMMARY OF FINDINGS:

The studies included for assessment in this prioritising summary update support those included in the original summary, in that ECT showed moderately satisfying effectiveness and safety in the treatment of cutaneous or subcutaneous malignancies, during short follow-up period. In addition, ECT dominated other treatment options with a favourable cost-effective ratio.

2008 HEALTHPACT ACTION:

Electrochemotherapy appears to be an effective method of treating subcutaneous melanomas. Further assessment of this technology is no longer warranted and

HealthPACT have recommended that this prioritising summary be disseminated to interested parties including the Clinical Oncological Society of Australia (COSA).

2008 SOURCES OF FURTHER INFORMATION:

Colombo, G. L., Di Matteo, S. & Mir, L. M. (2008). 'Cost-effectiveness analysis of electrochemotherapy with the Cliniporator(trademark) vs other methods for the control and treatment of cutaneous and subcutaneous tumors'. *Therapeutics and Clinical Risk Management,* 4 (2)**,** 541-548.

Curatolo, P., Mancini, M., et al. (2008). 'Successful treatment of penile Kaposi's sarcoma with electochemotherapy'. Dermatologic Surgery, 34 (6), 839-843.

Gaudy, C., Richard, M. A., Folchetti, G., Bonerandi, J. J. & Grob, J. J. (2006). 'Randomized controlled study of electrochemotherapy in the local treatment of skin metastases of melanoma'. *Journal of Cutaneous Medicine and Surgery,* 10 (3)**,** 115-121.

Larkin, J. O., Collins, C. G., Aarons, S., Tangney, M., Whelan, M., O'reily, S., Breathnach, O., Soden, D. M. & O'sullivan, G. C. (2007). 'Electrochemotherapy: aspects of preclinical development and early clinical experience'. *Annals of Surgery,* 245 (3)**,** 469-479.

Quaglino, P., Mortera, C., Osella-Abate, S., Barberis, M., Illengo, M., Rissone, M., Savoia, P. & Bernengo, M. G. (2008). 'Electrochemotherapy with intravenous bleomycin in the local treatment of skin melanoma metastases'. *Annals of Surgical Oncology,* 15 (8)**,** 2215-2222.

Snoj, M., Cemazar, M., Slekovec Kolar, B. & Sersa, G. (2007). 'Effective treatment of multiple unresectable skin melanoma metastases by electrochemotherapy'. *Croatian Medical Journal,* 48 (3)**,** 391-395.

WHO (1997). *Handbook for Reporting Results of Cancer Treatment, vol. 48,* Geneva, WHO, pp 22-27.

LIST OF STUDIES INCLUDED

Total number of studies	
Level II Intervention	1
Level IV Intervention	2
Case report	2
Cost-effectiveness analysis	1

PRIORITISING SUMMARY 2007

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):

- ☐ 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 — ARTG number
- ☒ No
- ☐ 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 Medpulser™ Electoporation 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-permeant[2] molecules into cells. This technique has been used *in vitro* to 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

Electrochemotherpay 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

[2] Permeant: able to pass through a semi-permeable membrane.

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 $3mm^2$ to $50mm^2$. 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 36[3] 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 (χ^2 =9.39, 1 df, p = 0.002) than the response rate in the group treated with bleomycin alone (31%) (Table 1).

[3] 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 (ESOPE[4]) 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.

[4] 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 electorporation 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. However, upon further consideration HealthPACT decided to monitor this technology in 18 months time.

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.

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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	1
Level IV Intervention	2

SEARCH CRITERIA TO BE USED:

Bleomycin/ therapeutic use
Cell Line, Tumor
Combined Modality Therapy
Electroporation/ methods