London Cancer Electrochemotherapy Guidelines

The aim of this document is to define the policy and procedure for the administration of Electrochemotherapy treatment (ECT) within London Cancer. Additional details are in appendices I-IV.

1. Introduction
ECT is a palliative treatment for patients with cutaneous and subcutaneous metastatic nodules regardless of primary tumour histology. The treatment has become established over the last 8-10 years, and was approved by NICE in 2013 (Interventional procedure guidance 446). The summary of the NICE guidance is:

There is sufficient evidence of efficacy of ECT for treating metastases in the skin from tumours of non-skin origin and melanoma to support its use as a palliative treatment. There are no major safety concerns. Therefore, in the context of palliative treatment the procedure can be used with normal arrangements for clinical governance, consent and audit.

- Patient selection should be carried out by an appropriate specialist multidisciplinary team.
- This procedure should only be carried out by a clinician with specific training in the technique.
- Clinicians should submit data on all patients undergoing ECT (including details of case selection, methods of follow-up and outcomes) to the InspECT register, an international register dedicated to ECT, and review clinical outcomes locally.

2. Background information
The principle of this local ablative treatment is to combine the administration of non-permeant or poorly permeant chemotherapeutic drugs eg bleomycin, with the application of electric pulses to the tumours in order to facilitate drug delivery into the cells. High-intensity electric field applications with short durations can allow intracellular manipulation and could be used to induce cancer cell apoptosis [1]. Furthermore, electrical pulses increase permeability, i.e. ‘electroporation’ thereby acting to enhance drug delivery and substantially potentiate chemotherapeutic effectiveness [2,3].

Electroporation can only facilitate drug transport of molecules through cell membranes that are poorly or non-permeant. As reviewed by Sersa et al [4], this restricts selection of chemotherapy to drugs that are hydrophilic, and lack transport systems in the membrane [4]. Indeed, most clinical data has been restricted to bleomycin, which has its action potentiated between 1000 and 5000 fold and cisplatin, which has its action potentiated from 10 to 80 fold by electroporation of cells [4,5]. The improved cytotoxicity of these agents is thought to be facilitated by a secondary consequence of ECT, vasoconstriction with endothelial disruption.

ECT results in a reduction in tumour blood flow that occurs in 2 phases. Firstly, a short-lived episode when the electric pulses are delivered resulting in a ‘vascular lock’ around the tumour cells that prevents wash-out of the cytotoxic agent and further concentrates the cytotoxic agents in the tumour cells. Secondly, the disruption of the endothelial cytoskeleton and intracellular junctions results in a change in the configuration of the surface of the endothelium. This leads to an impaired barrier function and interstitial oedema resulting in decreased intravascular pressure and compromised blood flow. Repair of the endothelium is slow and a reduction in blood flow in feeding tumour vessels is observed causing severe hypoxia to the tumour cells evident 5 days after treatment with ECT [5].

3. Indications for use
3.1 General principles
To be eligible for ECT patients need to:
Have either skin-only metastatic disease OR predominantly skin only metastatic disease with any non-skin disease small volume, asymptomatic and stable/slowly progressive only

Be unsuitable for standard local and/or the most effective systemic treatment options for that tumour type noting that:

- standard systemic treatment options will differ according to primary tumour type
- there is an element of discretion where ECT may be used ahead of some of the less effective palliative systemic treatment options where disease is skin only, especially in older or frailer patients where the toxicity of systemic treatments is considered less acceptable
- have a life expectancy of greater than 3 months
- be fit for the planned procedure - including general anaesthetic if being used, and for the planned chemotherapy agent given by the intended route (see below for intravenous bleomycin)
- have the mental capacity to consent to the procedure
- be 18 years or older - the procedure has not been validated in younger patients
- have adequate haematological function to reduce the risk of infection/bleeding complications
  - Neutrophils >1.5 x 10^9/L
  - Platelets >100 x 10^9/L
  - INR < 1.5

For those receiving intravenous bleomycin - the following requirements also apply:

- No previous history of pulmonary fibrosis, severe renal failure (GFR <10ml/min), allergy to bleomycin or cumulative bleomycin dose of >400000 IU/m^2
- Pre-treatment lung function tests essential (within 6 weeks of treatment), must have DLCO and KCO <1 SD from normal
- Pre-treatment CXR within 6 weeks of treatment, or chest CT within 3 months of treatment.

3.2 Caution/Relative Contra-indications:

- Presence of pacemaker in close proximity to area to be treated
- Patient on regular oral anti-coagulation - these will need to be converted from warfarin to LMW heparin prior to treatment
- Age > 70 and with impaired performance status or frailty
- Pre-existing pulmonary disease
- Prior/planned thoracic irradiation (will apply to most breast cancer patients)
- High dose oxygen exposure
- Smoker/ex-smoker
- Previous bleomycin cumulative dose >60 000 IU/m^2; patients must not exceed a total cumulative bleomycin dose of 400 000IU/m^2

3.3 Pre-treatment patient assessment to be completed </=7days before planned treatment and performed at Electrochemotherapy centre

Assessment for general anaesthesia if needed with any other tests anaesthetist deems necessary

3.4 Pre-treatment assessment of lesions/areas to be treated (at pre-treatment review AND on the day of treatment)

Assessment of number, size, depth and location of nodules to be treated, with clinical photography for reference, should be performed at initial assessment as well as on the day of treatment.
If there has been rapid progression of disease in the interval between initial assessment and treatment day a clinical decision should be made to whether treatment is appropriate, technically feasible and in the best interests of the patient.

4. Treatment

4.1 Chemotherapy agent and route of administration
There are 3 established chemotherapy schedules which have been used for ECT. However intra-lesion injections are used to treat small numbers of discrete lesions while intravenous bleomycin is used to treat more widespread diffuse lesions.

1. Intravenous bleomycin at a dose of 15 000 IU/m² given as a fast bolus over 30-60 seconds via a free flowing drip with normal saline
2. Intra-lesional bleomycin
3. Intra-lesional cisplatin

Intra-lesional drug doses are dependent on lesion size.

**Bleomycin:**
- Tumour’s < 0.5 cm³ - 1000IU/cm³;
- Tumour’s > 1 cm³ - concentration of 1000 IU/ml at the dose of 250 IU/cm³;
- Tumour’s > 0.5 cm³ < 1 cm³ - 500 IU/cm³ [2]

**Cisplatin:**
- Tumour’s > 1 cm³ - 0.5 mg/cm³ of Tumour;
- Tumour’s > 0.5 cm³ and < 1 cm³ of 1 mg/cm³ of Tumour;
- Tumour’s < 0.5 cm³ - 2 mg/cm³ of Tumour [2]

4.2 Chemotherapy prescribing and administration
All personnel involved in the ECT procedures must adhere to the current local and Pan-London cytotoxic policies. Chemotherapy may only be prescribed by an authorised prescriber and generated using the relevant electronic prescribing system. Intravenous chemotherapy doses may only be administered by appropriately trained nursing staff or individuals with chemotherapy administration privileges. An extravasation kit and chemotherapy spillage kit and chemotherapy waste bin must be available in theatre prior to administration. The doses of chemotherapeutic drugs used during ECT are based on the patient’s body surface area calculated by the Dubois formula.

4.3 Choice of anaesthetic
Both local and general anaesthetic have been used for patients irrespective of the chemotherapy schedule in use. In general patients with extensive and multiple nodules to be treated may be better with a general anaesthetic but the choice for an individual patient is up to the treating team and patient (see appendix I)

4.4 Delivery of Electrical Pulses, pulse parameters, frequency
Electrical pulses are delivered using cliniporator™ according to manufacturer’s guidelines and via specifically designed electrodes which are in contact with the patient’s skin in the area to be treated. Treatment begins 8 minutes after chemotherapy drug administration.

4.5 Pain Relief and post-operative care
Pain control and monitoring is a requirement of treatment and also in the post treatment period. Patients may be admitted for observation, wound-care and pain relief following the procedure if required, otherwise they are treated as day patients. Patients will be discharged with information regarding wound care and details of a point of contact if there are any problems after discharge (see appendix II)
5. **Follow-up**
Patients should be followed up at the discretion of the clinician. For many patients, further follow-up at their local centre, with re-referral in the case of complications and/or progressive disease may be most practical (see appendix III).

6. **Repeat Treatment/s**
Treatments can be repeated at intervals of not less than 4 weeks for either completion of treatment not possible in one session, or the treatment of recurrent/new lesions which appear after previous treatments.

For patients planned to have repeat treatments, it is important to ensure that the overall disease status remains appropriate (repeat staging if >3months since last done) and that (for intravenous bleomycin) lung function tests are repeated and remain adequate. Total cumulative intravenous bleomycin dose must not exceed 400 000IU/m².

7. **Adverse events to treatment**
Any adverse events occurring during bleomycin administration, administration of pulses or within 24 hours of treatment which results in serious injury or death must be recorded in the patient notes and submitted to the inSpECT database.

8. **DATA submission to inSpECT database**
Records should be kept of all consultations pertaining to the referral for ECT and if ECT is declined the reasons for this should be documented in the patient notes. All patients who receive ECT should be entered into the InSpECT registry to facilitate the audit of complication related to the procedure. This is the responsibility of the tertiary unit performing the treatment.

All deaths within one month following ECT should be recorded and the case reviewed at a morbidity and mortality meeting at the treating centre.

9. **Referral and Treatment Pathways**
9.1 **Treatment Locations**
Two tertiary treatment centres have been identified within London Cancer: Royal Free London (RFL), Hampstead site and BARTS Health NHS Trust – Royal London site. Treatment can be offered to patients from within and outside the London Cancer area.
At BARTS Health, ECT procedures are carried out by Mr Graeme Moir, Consultant Plastic surgeon, with the ECT chemotherapy prescribed by oncologists Dr Virginia Wolstenholme and Dr Peter Szlosarek.
At the Royal Free, procedures are carried out by Prof. Mo Keshtgar, Consultant Surgical oncologist, and the chemotherapy prescribed by Dr Jackie Newby and Dr David Chao.
It has been agreed that BARTS will lead for patients receiving ECT for head and neck tumours and melanoma; RFL for patients with breast cancer. However, patients already under oncology at either centre should remain at their base centre regardless of tumour type to be treated.

9.2 **Referral pathways**
Referrals may be received from a variety of sources. Ideally, the referral for ECT for a specific patient should have been discussed by their local MDT before the referral is received. As a minimum, where the referral is received from another source (e.g. surgeon/GP), evidence that the patient’s oncologist is in agreement with the referral should be sought in all instances.
At RFL, referrals should be addressed to Prof Mo Keshtgar/Dr Shramana Banerjee via their secretaries. At BARTS, referrals should be addressed to Mr. G. Moir/ Dr. Virginia Wolstenholme via their secretaries. Once received, referrals will be co-ordinated by a designated member of the team to gather requisite information, arrange for MDT discussion and if appropriate, arrange joint ECT clinic appointment. The following information should be sought for all potential patients in order for the tertiary centre to evaluate the probable suitability of the treatment for the patient:

- Current treatment regimen AND all previous treatments following diagnosis
- All histopathological information since diagnosis
- Most current staging investigations, which should be within last 3 months, if not, up to date imaging should be requested, ideally done locally
- Confirmation that either the referral has been authorised via a local MDT and/or the local oncologist feels that the referral is appropriate
- Any key co-morbidities

10. References

2. Mir LM, Gehl J, Sersa G et al. Standard operating procedures of the Electrochemotherapy: instructions for the use of bleomycin or cisplating administered either systemically or locally and electric pulses delivered by the Cliniparator by means of invasive or non-invasive electrodes. EJC Supplements 2006; 4: 14-25.

Appendices

APPENDIX I – Anaesthetic choices
If general anaesthetic to be used, the anaesthetist must be aware of the risks of using high dose oxygen with respect to intravenous bleomycin and pulmonary toxicity. As each ECT pulse is very brief (<100μs) and the whole procedure is short (<30min) and since residual pain is moderate, reversible drugs are desirable for sedation (e.g. propofol) and analgesia. Volatile agents and nitrous agents should be avoided. Airway control should be secured before bleomycin infusion. Premedication with sedatives is not necessary with general anaesthesia. The main risk is respiratory depression due to excessive sedation and analgesia; it may require transient assisted ventilation for a few minutes.

APPENDIX II – Pain relief and post-operative care
As per local protocols. These may be used as a guide if needed:

Pre-op considerations
- Pre-operatively, patients with no pre-existing painful areas/lesions should be given 300mg-600mg of gabapentin and this should be continued in the immediate post-operative period twice daily until review at 4 weeks post treatment.
• Patients who are known to have pre-existing pain at pre-treatment assessment should be commenced on gabapentin 300mg-600mg at pre-treatment assessment until 4 weeks post treatment review
• Patients with renal impairment will require a reduced dose of gabapentin or alternative medication and expert consultation should be sought with pharmacy and pain management team with regard to the appropriate dose or medication as a part of pre-treatment planning

**Immediately post treatment**
• After treatment, a kaltistat™ dressing covered with instilage™ is placed over all the treatment areas and then a further loose dry dressing will be applied over the treated area
• Patient returned to ward with PCA of morphine/opioid analgesic in syringe drive apparatus. Patient is prescribed regular anti-emetics and gabapentin plus simple analgesics as required

**Ward care in the first 24-48 hours**
• 4 hourly measurements of temperature, heart rate and blood pressure are monitored throughout in-patient stay
• 6 hourly pain score recording should be made on PCA chart during in-patient stay and this should be continued by patient twice daily until their review post-operatively. A pain diary may be provided for this
• Before discharge the ECT proforma should be completed by the surgical team
• Patients should be discharged when deemed medically well and symptoms of pain/discomfort can be controlled with oral medication.

All patients must have the contact details of a named CNS.

**APPENDIX III – follow up**
• To review the development of potential complications photographs of the treated areas should be taken pre-and post-treatment to facilitate monitoring of treatment
• Pulmonary function tests should be repeated if patients experience any breathing difficulties after the procedure and also prior to any further treatment planning. Ideally this should be performed 6 weeks or more after the first treatment if a further treatment is to given as this should allow enough time for resolution of pain related to treatment which might otherwise impair their performance
• Patients should be offered physiotherapy sessions and allied support according to their needs soon after discharge at their local hospital and this should continue until the patient has regained most of their level of exercise tolerance prior to treatment. The treatment should include breathing exercises if appropriate
• Where appropriate, attention should be paid to the nutritional intake/habits of the patient to promote good nutritional balance in order to facilitate wound healing.