We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

The Role of Electrochemotherapy in the Treatment of Malignant Melanoma

Mecker G. Möller¹, Slawomir Salwa²,
Declan M. Soden² and Gerald C. O'Sullivan²

¹*Division of Surgical Oncology, Department of Surgery, University of Miami,
Miller School of Medicine, Miami, Florida*

²*Cork Cancer Research Centre, Leslie C. Quick Laboratory, BioSciences Institute,
University College Cork and Department of Surgery, Mercy University Hospital, Cork,*

¹USA

²Ireland

1. Introduction

About 68,130 new melanomas will be diagnosed in the United States during 2010 (38,870 men; 29,260 women) and of those 8,700 people will die of the disease (5,670 men; 3,030 women). The death rate has been dropping since the 1990s for those younger than 50, but has remained stable or is rising for older individuals. However, the incidence of melanoma has been increasing for at least 30 years, and this trend has become more pronounced in young white females and in older white men¹.

Malignant Melanoma is the seventh most common type of cancer, but it is the first cause of death from cutaneous skin cancers². It has been estimated that the lifetime risk of developing malignant melanoma is 2% (1 in 50) for Caucasians, 0.1% (1 in 1,000) for those of black descent, and 0.5% (1 in 200) for Hispanics³.

When melanoma is detected in advanced stages, it carries a dismal prognosis, with a mean survival of about 8 months and a 5-year survival as low as 5%⁴⁻⁶. The disease spreads both by the lymphogenous and the haematogenous routes and can metastasize to virtually any organ in the body. When secondary tumours emerge, these usually follow a sequential pattern to regional lymph node basins, followed by distant sites including skin, subcutaneous tissue, lung, liver, brain, bone and other viscera⁵⁻⁶. Local recurrence, in-transit metastases and satellitosis (cutaneous metastases within 2 cm of original lesion) represent the same dissemination process⁴ in the dermal lymphatics. When the patients present with cutaneous metastases, they are considered to have stage IIIB disease⁷. Cutaneous metastases occur in 2-20% of patients, depending on tumor thickness^{6, 8-9} and can occur either during the early or late phase of the disease¹⁰. In many instances they can represent the first site of recurrence after surgical excision of the primary tumor¹¹. The majority (70-80%) of recurrences are diagnosed within the first 3 years of initial diagnosis, and the median time to the presence of in-transit disease could range between 3 to 16 months⁴. The recurrences present as local or in-transit disease in 20-28%, regional disease in 26-60% and as distant metastases in 15-50% of patients. Even though local recurrence is

not yet considered stage IV disease, the prognosis is poor with 5 year survival rates of less than 50%^{9,12}. The risk of developing metastases may be predicted at excision of the primary lesion and determinants include, increasing thickness of the tumour, the anatomical location, histological subtype and gender¹³. In general tumours of the trunk, non cutaneous and subungual regions behave more aggressively than those of the extremity¹⁴⁻¹⁶.

2. Treatment limitations for recurrent or in-transit melanoma

Treating extensive cutaneous/subcutaneous nodules or in-transit disease is a clinical challenge because of common unresectability and relative insensitivity to conventional systemic therapies⁶. These recurrences provide a significant psychological burden for patients whose quality of life is negatively affected by the symptoms caused by the tumor, such as pain, bleeding, ulceration, and malodorous discharge^{4, 17-18}. Many patients suffering from in-transit disease also manifest with systemic disease, within 6-13 months of the onset of the local lesions. Their life expectancy is foreshortened and is determined by factors such as the burden of the loco-regional disease, the interval from initial treatment and their immune status⁴.

The aim of the treatment should be the elimination of both local and systemic disease with the benefit of improved life expectancy and quality of life, while minimizing toxicities or deformities. It is important to note that metastatic cells have disseminated prior to surgical intervention, outlining the critical need for the development of adjuvant therapeutic strategies¹⁹. Thus the treatment of unresectable and in-transit disease is both systemic and loco/regional. The options include surgery, which is the most effective method for limited recurrent or in-transit disease, systemic chemotherapy^{12,21}, radiation therapy²², cryosurgery²³; carbon dioxide laser ablation,^{12,24-26} intralesional therapies^{12,21} with the Bacille Calmette-Guerin vaccine²⁷, TNFerade a non replicant adenovirus complex, expressing the Tumor Necrosis Factor alpha (TNF- α) gene (hTNF- α cDNA)^{12,28}, and Interleukin-2²⁹, Cell Vaccine and Immunotherapy³⁰⁻³³, Interferon alpha³⁴⁻³⁶, Regional therapies such as hyperthermic isolated limb perfusion (HILP) and Isolated limb infusion (ILP)³⁷, Novel Molecular Therapies with c-Kit inhibitors (Imatinib), C-RAF-inhibitors (Sorafenib)³⁸, and blocking B-RAF regulation of mitogen-activated protein kinase pathway (MAPK)³⁸. In more recent years electroporation with anticancer drugs which is termed electrochemotherapy (ECT) has been successfully applied for local tumour control^{17, 19, 39}. In general malignant melanoma is refractory to systemic treatments and survival after treatment of regional cutaneous metastases has been reported to be between 20-28% at 10 years^{6,9,40}. However all current treatment modalities have individual limitations and variable response rates^{4, 12, 19, 41-42}.

3. Electrochemotherapy (ECT)

Definition and physiological effect:

The cell membrane represents a physical barrier to the intracellular transfer of hydrophilic drugs, macromolecules, nucleotides and peptides. The movement of polar and hydrophilic molecules across the membrane is restricted by the phospholipid bilayer¹⁸. Studies suggest that exposure to sufficiently strong and long electrical fields, could rearrange the lipid bilayer, by reorienting the hydrophilic heads in pore-like fashion, while the hydrophobic

tails are embedded within the plasma membrane. This porosity is transient and reversible if short duration high amplitude square wave electrical pulses are optimized.¹⁸

Electroporation (EP) of tumour nodules allow the permeation, into the cancer cells, of poorly permeable antineoplastic drugs, such as bleomycin or cisplatin which are given either systemically or intratumorally (IT)^{18, 39, 43-46}

The temporary permeability of the cell membrane caused by the electric pulses facilitates a potent localized effect and magnifies the drugs cytotoxicity by orders of magnitude ^{18, 39, 46-50}.

Types of Drugs

After several studies of different cytotoxic drugs, two have been identified as the best candidates for ECT: Bleomycin and Cisplatin ^{17, 45}. Of importance in these studies EP or the drugs on their own do not influence the growth of tumours, yet their combination have potent tumoricidal effects^{18, 51-53} (See Figure 1). An advantage of ECT is that it requires much lower doses of the cytotoxic drug for optimal effects than those usually used for systemic treatments. In addition there is little in the way of collateral damage or complications, since the the cell killing is confined to the tissues affected by the electric field. Bleomycin intercalates into the cellular chromatin causing single and double stranded breaks in DNA resulting in a mitotic cell death by pseudoapoptosis. (Figure 1 B,C & D). On the other hand, Cisplatin creates an apoptosis effect on the cell ^{18, 46}. This cytolytic activity is potentiated more than 1,000 fold for Bleomycin and 100 fold for Cisplatin by the addition of EP ^{12, 19, 48-49}.

The Vascular Lock

The electric pulses produce a transient state of hypoperfusion by local reflex vasoconstriction at the arteriolar level (lasting 1-2 minutes) and a phase of interstitial edema (that resolves with membrane resealing). However the effect may last longer (12 hours to 5 days) in rapidly dividing tumor cells and is more prominent in tumours with a less mature endothelial lining and higher interstitial pressure. This phenomenon mediated by the sympathetic nervous system is termed the “vascular lock” and it has implications for timing of drug administration¹⁸⁻¹⁹. After application of the electric current, there is a retention of drugs already in the tumour but there is also an impairment of entry of drugs from the circulation. Thus when the cytotoxic drugs are administered systemically sufficient time should be allowed to achieve optimal intratumoral drug concentration prior to application of EP. ECT produces other vascular influences, which are believed to be secondary to a reduction in local angiogenic factor production, such as endothelial cell destruction and neovascular reorganization ^{46, 54-55}. The combined vascular influences have been successfully exploited in the treatment of bleeding melanomas ⁵⁶⁻⁵⁷– which may be a difficult to manage problem, sometimes refractory and fatal, in patients with unresectable disease.

4. Technique of electrochemotherapy

1. The Equipment

The electric pulses may be applied to the tumors either by plate electrodes on the skin surface or by needle electrodes inserted into the lesion (figure2). The electric field distribution is determined by the geometry of the electrodes. Regardless of the type of electrode the electric field is highest around and between the electrodes ¹⁷⁻¹⁸. The current pulse generators in use are the Cliniporator (IGEA, Carpi, Italy) (FIG 2) and the Medpulsar™ (Inovio Biomedical Corporation, CA, USA). It appears that plate electrodes are

Fig. 1. A. Growth curves of experimental cancers in mice, which demonstrate that electropermeabilisation or intratumoural bleomycin alone, have no influence on tumour growth but when used together completely ablate the tumour. B) Positive TUNEL stain 48 hrs post ECT indicating tumor cell death by apoptosis. C & D Tumour before showing normal cellularity and D 48 hrs post ECT showing regions of denudeation

more suitable for use in superficial skin lesions, while needle electrodes are used for deeper seated lesions, such as exophytic and thick lesions (maximum depth 3 cm)⁵². A disadvantage of plate electrodes over the needle type is the potential skin damage that may be generated by the higher impedance/resistance of the skin, especially when treating larger affected areas^{19, 58}. Care must be taken to avoid inserting the needle electrodes into the healthy tissue surrounding the tumors, which may also result in local subcutaneous burns ³⁹. There are three types of electrodes in common usage (*FIG 2*). Type I electrodes consist of two parallel stainless-steel plate electrodes, used for superficial lesions and do not penetrate the skin. Type II electrodes are used for smaller lesions and consist of two rows of eight needles with 4 mm distance between them, while Type III electrodes are recommended for larger lesions (>1cm), with the needles in a hexagonal configuration. The needles are inserted encircling the tumor and down to the subcutaneous tissue, slightly deeper than tumor depth ^{17, 19, 52, 59} . It is recommended to elevate or tent the skin at the time of delivering the electric current , if the electrodes are to be inserted in a superficial or shallow subcutaneous areas such as near the knees, tibial tuberosities, the scalp, or close to any other osseous structures⁵²

Fig. 2. (A) The ECT pulse generator. B) Note an entrainment of 8 square wave pulses. C) Electrodes type1 (plates) and (D) type 3 (Needle array).

2. Anesthesia

The procedure can be performed in the outpatient or ambulatory setting, under local anesthesia in association with conscious sedation. General anesthesia may be preferred for larger tumors, or tumors located in prior irradiated or fibrotic tissues where infiltration of local anesthetic may be painful and less likely to diffuse and thus achieve adequate pain control and for those located too close to vascular or bony structures. The dose of local anesthetic should be recorded and should not exceed the maximum allowed per body weight for Lidocaine without epinephrin (3 mg/kg)^{52, 59-60}. In addition, a mixture of O₂/air with FiO₂ of 40 % is administered to the patients during conscious sedation.

3. The Electric Current

Permeabilization occurs in the cell when the internal transmembrane potential has surpassed the critical value between 200-300mV. The extent of the electroporative effect depends on the number and duration of the electric pulses^{18,55}. Two pulse parameters have been evaluated - exponentially decaying pulses and square wave pulses. Of the two, square wave pulses are preferred as they permit independent control of the length and amplitude. The pulse parameters selected for treatment depend on the type of electrode^{18, 52}.

Pulse parameters

Ideally for Type I (plate) electrodes, pulse parameters of 8 square waves with amplitude of 1300 V/cm, duration of 100 μ s, and frequency of 1Hz are used. The current should be delivered in two perpendicular directions.

For type II (needle) electrodes the voltage amplitude may be reduced to 1000V/cm. The pulses are administered simultaneously between the needle pairs.

For Type III, the needles are positioned hexagonally and 96 pulses are given together (12 pairs x 8 pulses) at a frequency of 5 kHz⁶¹.

Due to the already described vascular lock phenomenon, it is recommended that the electric current is applied between 8 to 28 minutes after IV administration of the drug⁶², or immediately (within 2-10 minutes) after intratumoral administration^{19, 59, 63-64}.

4. Drug Dosage Recommendations

Initial studies compared the routes of administration of Bleomycin suggested advantages for the intralesional over intravenous administration (77% vs. 45 % complete responses)⁴⁵ but later the prospective multi-institutional ESOPE (European Standard Operating Procedures of Electrochemotherapy) study in 2006, concluded that IV or IT Bleomycin were comparable when given to tumors of volumes less than 0.5 cm³⁵². For Cisplatin, the studies have shown that IT is more effective than the IV route, with CR rates of 82% vs. 48% respectively^{19, 45}. In the ESOPE study local tumor control was achieved in up to 88% of tumors treated with IV Bleomycin, 73% with IT Bleomycin and 75% with IT Cisplatin⁵².

If a lack of uniformity of drug distribution within the tumor is anticipated either by the presence of large and extensive disease, harder fibrotic tumor nodules, lymphedema or limb fibrosis, the IV route would be more suitable⁵². The Intratumoral route is more feasible for those less perfused nodules located in previously pretreated areas¹⁹.

When Bleomycin is given IV the dose is 15,000 IU/m² of body surface area in a bolus lasting 30-45 seconds. But when the IT route is chosen, both drugs are given in a dose calculation based on tumor burden. The IT dose of Bleomycin based on tumor size is calculated as follows: for tumor nodules less than 0.5 cm³ a dose of 1000 IU/cm³, tumor nodules between 0.5 and 1 cm³ a dose of 500 IU/cm³ and for tumors larger than 1 cm³ a dose of 250IU/cm³ is

administered. The cumulative dose should not exceed 400,000 IU/m² due to the cumulative risk of lung fibrosis^{46,52}. If the cumulative dose surpasses 60,000 IU /m², objective respiratory function tests should be made at intervals and the drug discontinued if the respiratory diffusion capacity is abnormal⁶⁰. The IT dose of Cisplatin is given as follow: for nodules less than 0.5 cm³ a dose of 2mg/cm³, for nodules between 0.5-1 cm³, a dose of 1mg/cm³ and for nodules larger than 1 cm³ a dose of 0.5mg/cm³ is given. (Table 1)

Tumor Volume (V=ab ² π/6)	Bleomycin dose (1000 IU/mL concentration)	Cisplastin dose (2mg/mL concentration)
<0.5 cm ³	1 mL/cm ³ tumor 0.5 mL/ cm ³ tumor 0.25 mL/ cm ³ tumor	
>0.5 < 1 cm ³		
>1 cm ³		

Table 1. Tumor volume and IT drug dose concentration

The rationale for reducing the intralesional dose per cm³ when treating areas with larger tumor burdens is to reduce the risk of systemic toxicities of the absorbed drug without compromising local efficacy¹⁹.

Prophylactic antibiotics against skin flora should be given intravenously prior to the start of the procedure, especially when lesions are ulcerated or necrotic.

The required time for the procedure is short, with a median treatment duration of 25 minutes³². Repeated treatments are usually well tolerated by the patients ^{11, 65-66} and these can usually be performed at 1-6 weekly intervals, without evident resistance ⁴⁵.

5. Patient monitoring

Prior to each treatment session patients should have an electrocardiogram (ECG), blood work for evaluation of renal function, coagulation and electrolyte values. All lesions should be photographed and the tumor burden documented. Cellular debris may be released from the tumour during electroporation and these may interfere with the clearance of cytotoxic drugs by the kidney. Thus, when using IV Bleomycin, the serum creatinine should be maintained at less than 150mol/L to ensure proper renal clearance. Physiological monitoring includes visual display of O2 saturation, pulse rate, blood pressure, continuous ECG tracing and respiratory parameters. Acetaminophen or an anti-histaminic medication may be given to prevent the mild febrile reaction that may occur in the early post procedural period when Bleomycin is administered ^{46, 59}.

Technical pearls

1. Test the device and the electrodes prior to beginning the procedure
2. Prep and drape following sterile technique principles
3. Keep in mind correct timing of drug administration and application of the electric current
4. Protect osseous surfaces by tenting the skin
5. Communicate with awake patients and assisting staff, prior to delivery of electric current
6. Check electroporator traces and waves to confirm proper current delivery
7. Do not overlap treating fields with normal tissue
8. Dress wounds according to presenting symptoms

5. ECT development and clinical applications in melanoma

Neumann in 1982⁶⁷ published the first paper regarding EP as a method to transfer genes into mammalian and bacterial cells. There were other *in vitro*^{65, 68} and *in vivo* studies in early and late 1980's using EP in combination with drugs⁶⁹, but the first clinical trials demonstrating its effectiveness over Bleomycin alone for the treatment of a diversity of cutaneous tumors of the head and neck region, were published in early 90's by Mir et al.⁴⁷ and Belehradec et al.⁷⁰ from the Institute Gustave Roussy, in Villejuif France. These first 8 patients were treated for squamous cell carcinoma tumors and a complete response (CR) was observed in 57% of the lesions. These early publications encouraged other investigators to expand the principles of this technique to other tumor types including basal cell carcinomas, Kaposi sarcoma, and melanoma metastases^{6, 62, 71-74}. By the mid 90's, Rudolf et al.⁷¹ and Heller et al.⁷³ published the results of an initial small group (5) of melanoma patients that underwent treatment with ECT and IV Bleomycin. They reported overall response rates (OR) in 92% and 50% of 24 and 10 metastatic nodules respectively¹⁹. That same year, Glass et al.⁷⁵ from the University of South Florida in Tampa, USA, reported on the first study using ECT with IT Bleomycin in melanoma metastases obtaining OR rates of 92% (78% CR and 14 % PR) in 20 metastatic lesion – results similar to those obtained by the IV route in the previous studies. Later in 1998, the same group of investigators published the results of a bigger cohort of patients with a variety of cutaneous and subcutaneous malignant nodules. Twelve of 34 patients had 84 metastatic melanoma nodules with documented OR rates up to 99% (89% complete response (CR) and 10 % partial response (PR))⁷⁶. That same year, the combined data produced by five institutions in USA, France and Slovenia was published by Mir et al.³⁹ In this study, twenty patients with metastatic melanoma lesions showed responses in 131 (92%) of 142 lesions, with CR of 53% and PR of 39%. A major finding of this study was that the results were comparable among the institutions even though their treatment protocols and the route used for administering the Bleomycin were not standardized. Additional small studies^{56, 77-79} using ECT with IT Bleomycin for melanoma lesions continued to show good responses, with OR rates of 71 to 100% (CR 23%-100% and PR 0%-62%). Rols et al.⁸⁰ in 2000 continued to demonstrate OR's of 93% using ECT and IV Bleomycin in the treatment of 54 metastatic melanoma nodules.

Sersa et al.⁸¹⁻⁸² introduced Cisplatin as a therapeutic option in 1998. In their studies they reported CR rates of 100% for 2 patients with 13 lesions treated with IT Cisplatin, but low CR rates of 11 % in 9 patients with 27 lesions treated using the IV route. Additional studies were published using this drug by the IT route only^{61, 82-83} with OR rates ranging from 81% to 100% (CR 0%-70 % and PR 6%-100%).

The main issue with most of the studies of the 1990's and early 2000's was the utilization of a variety of treatment protocols with different pulse parameters and pulse generators in combination with different electrode types and drug administration routes^{6, 39, 44, 47, 52, 56, 58, 63, 70, 72-73, 75-78, 81-88}. But in 2006 the results of a pivotal prospective non-randomized multicenter ESOPE study⁵² were published, thus providing recommendations for a standardized protocol for the procedure. The study included 102 patients, 61 evaluated for response and 41 for toxicity respectively. The protocol allowed for administration of Bleomycin either IV or IT, or with Cisplatin IT, and included several histological types of lesions. Ninety-eight lesions from 20 melanoma patients were evaluated - The OR rates were 81% with a CR of 66%. The results confirmed the effectiveness of ECT in the treatment of lesions of different histology, demonstrating an 85% objective response rate and a CR rate of 74% for all lesions.

These results were independent of the drug used or the route of administration chosen. Additionally subsequent studies^{11, 49, 66, 89-92} of ECT evaluating its effect in the treatment of melanoma and other skin cancers continue to demonstrate the efficacy of the treatment, with response rates comparable to the earlier studies, ranging from 46-100%.

Repeated treatments are feasible as demonstrated by Campana et al.⁹⁰ and Quaglino et al.¹¹ producing additional clinical responses in patients who had initial non or partial responses or who presented with new recurrent lesions. In the Campana⁹⁰ study 34 patients out of 52 were diagnosed with unresectable melanoma, but the response rate for the entire cohort of patients treated with either IT or IV Bleomycin improved significantly from a CR of 50%, up to 83 % after the third ECT treatments.

There are approximately 60 institutions in Europe and in the United States that continue to investigate and offer ECT as a palliative treatment for a variety of unresectable tumors, including melanoma; and in an occasional report it has been used as an alternative curative therapy⁹³.

6. ECT in the treatment of advanced melanoma

In patients with unresectable recurrent or in-transit melanoma disease who are not candidates for standard surgical or medical treatment, ECT is now an important therapeutic option^{18,43,49,75,84,94}. These cases include those with unresectable disease due to the extensive number of nodules or lesions located in compromising anatomic areas, such as those around joints, nerves, distal leg and in previously operated fields. Encouraging results with long term remissions have been documented^{17, 45, 78, 93, 95-96}. (Figure 3)

Fig. 3. A) An Exophytic type recurrent malignant melanoma after isolated limb perfusion. B) Six months following treatment by ECT .

Author	No. Patients	Nodules	Drug/route	CRR %	ORR (PR+CR)%
Rudolf 1995 ¹³⁵	2	24	Bleomycin IV	92	92
Heller 1996 ¹³⁷	3	10	Bleomycin IV	30	50
Glass 1996 ¹⁴⁰	5	23	Bleomycin IT	78	96
Heller 1998 ¹⁴¹	12	84	Bleomycin IT	75	99
Kubota 1998 ¹⁴⁴	1	8	Bleomycin IT	100	100
Mir 1998 ²⁷	20	142	Bleomycin IV	53	92
Sersa 1998 ¹⁴⁶	2	13	Cisplastin IT	100	100
Sersa 2000 ¹⁴⁷	9	27	Cisplastin IV	11	48
Sersa 2000 ¹⁵³	10	82	Cisplastin IT	80	87
Rols 2000 ¹⁴⁵	4	55	Bleomycin IV	9	93
Gehl 2000 ¹²⁸	1	9	Bleomycin IT	100	100
Rodriguez 2001 ¹⁴³	2	13	Bleomycin IT	23	85
Sersa 2003 ¹⁴⁹	14	211	Cisplastin IT	70	81
Byrne 2005 ¹⁴⁴	21	52	Bleomycin IT	63	71
Snoj 2005 ¹⁴⁸	1	1	Cisplastin IT	0	100
Marty 2006 ¹²⁴	20	98	Bleomycin IT/IV* larger 3 cm	66	81
Gaudy 2006 ¹⁵⁹	12 (7 per protocol)	30	Bleomycin IT	36	46
		23		74	82
Snoj 2006 ¹⁶⁵	1	16	Cisplastin IT	100	100
Larkin 2007 ¹²¹	4 (2 pts LTF)	56	Bleomycin IT or IV for nodules > 3 cm	0	50
Snoj 2007 ¹⁶⁴	1 (RETC x4)	224	Bleomycin IV	100	100
Tauceri 2007 ¹⁵⁷	3	ns	Bleomycin IT	ns	ns
Qualigno 2008 ¹²	14 (7 pts RETC)	160	Bleomycin IV	50	93
		73		58	93
Campana 2009 ¹⁵⁸	34 MM *(52 cohort 27 RETC)	373	Bleomycin IT/IV	ns	ns
		608		50	74
		257		66	90

IV: Intravenous, IT: Intratumoral, CRR: Complete Response Rate, ORR: Overall Response Rate, PR: Partial Response, CR: Complete Response
RETC: Repeated Electrochemotherapy, LTF: Lost to follow up, ns: No specified, MM: Malignant melanoma
*: Patients with different histological types

Table 2. Summary of most relevant studies using ECT for unresectable or In-Transit Melanoma

Its effectiveness has been proven when providing palliative treatment for hemorrhagic and painful tumor nodules^{56-57, 79, 97-98}. This is a benefit believed to be secondary to the “vascular lock” phenomenon. The vasoconstriction at the arteriolar level produces an immediate and dramatic reduction of perfusion of the malignant lesions, thus controlling the bleeding^{18, 45, 98}. ECT can also be useful as a neoadjuvant treatment for cytoreduction and organ sparing treatment. Its benefits have been reported in patients with perineal melanoma treated with Cisplatin⁸⁵ and for a sphincter saving procedure in anal melanoma⁸³.

ECT can also be suitable for and more tolerable by those patients with a prohibitive surgical risk due to significant comorbidities⁵² because the length of the procedure is relatively short⁵² and patients are able to tolerate multiple sessions. In some anatomical locations ECT could provide good and sometimes better cosmetic results than surgery⁹³.

ECT in combination with cytokine therapy or gene coding immunotherapies has advanced to clinical trials in advanced melanoma. In a phase II study, patients treated with injections of low dose perilesional IL-2 and ECT with Bleomycin, the cytotoxic T lymphocytes response against the known melanoma antigens initially decreased after treatment to reappear when IL-2 was stopped. The tumor-specific peripheral T cells could be detected later in the lesions. The authors theorized that cell death produced by ECT may have attracted and primed dendritic cells with the tumor antigens, which later migrated to the draining lymph node basin, and elicited a T cell response against those antigens expressed by the melanoma¹⁰⁰.

The first Human phase I trial of *in vivo* DNA electroporation of recurrent malignant melanoma was published in the USA in 2009¹⁰¹. EP with dose escalation of the interleukin-12 plasmid (*in vivo* DNA EP) was used in the treatment of 24 patients with stage III B/C or IV disease. It resulted in significant necrosis of melanoma cells and regression of the majority of treated lesions. In addition, clinical regression of untreated lesions suggested the induction of systemic anti tumor immune responses. The treatment was found to be safe with no significant reported toxicities. While additional studies in larger cohorts of patients are still necessary, to obtain reproducibility of these results, these data show a new method of inducing potent tumour specific immune responses individual to the patient.

There are no studies comparing ECT with other surgical modalities, however when taking into consideration the learning curve of other complex regional treatment modalities, the techniques of ECT are considered to be “user friendly” and easy to teach and learn. This technique can also be highly advantageous and useful in countries or hospitals where other modalities or resources are limited.⁴⁵

7. Advantages of ECT

1. Excellent local tumor control rates (80-90%)
2. Minimal risk of damage to healthy surrounding tissue
3. Lower chemotherapy doses needed, minimizing the toxicity profile of the drug
4. There is no protein denaturation, which may elicit an undesirable immune response against self antigens
5. High safety profile without severe side effects
6. Good cost/benefit ratio profile: ambulatory setting, lower cost for drugs, and minimal equipment needed.
7. Treatments are well tolerated by patients
8. Improvement in the perceived quality of life

8. Patient selection and limitations of the procedure

The contraindications of the ECT could be divided into drug and procedure related.

A. Drug related contraindications⁶⁰:

1. Known allergy to the drug to be administered
2. Interstitial lung fibrosis, if Bleomycin is going to be used
3. Kidney failure or limited renal function
4. When the cumulative dose of Bleomycin has reached $>400,000 \text{ UI/m}^2$

B. Procedure related contraindications⁴³:

1. For safety reasons ECT should not be used in patients with implanted electric devices such as pacemakers
2. In patients who may carry a higher risk of bleeding such as those on anticoagulants or with increased INR and platelets count $< 70,000$.

9. Limitations

With the current available electrodes, ECT has limitations when treating deep seated tumors⁴³. Tumors larger than 3 cm^2 appear to have lower response rates (CR 73 %) to ECT^{11,49,90} as compared to nodules smaller than 1 cm^2 (CR 98%). These findings were not affected by either the cutaneous or subcutaneous location of the nodules¹¹.

When tumor nodules are located in irradiated or fibrotic tissues the needle electrode penetration may be problematic with a suboptimal delivery of the electrical current or drugs⁹⁰. Nonetheless, if optimal needle penetration is achieved, ECT is equally effective in irradiated as in non-irradiated tissue⁵². If extensive disease (more than 15 lesions) is present repeated sessions may be necessary. In aggressive disease – while undergoing ECT new cutaneous nodules may emerge but palliative retreatment is worthwhile even though the systemic disease progresses rapidly⁶⁰.

This treatment modality has not been studied in randomized trials with other treatment techniques, such as ablative and perfusion or infusion procedures, or radiation therapy. More studies with longer follow up are still needed to evaluate disease free survival and to compare ECT to surgical excision, not only in the palliative setting but as a curative alternative in those patients unsuitable or unfit for a surgical procedure¹⁹.

10. Toxicity and side effects

ECT has a low toxicity profile with limited side effects as compared to other regional therapies such as HILP or ILP⁴¹. However one of the limitations of fully assessing the toxicities of the treatment is the inconsistency of the large majority of the published studies documenting complications.

The systemic dose of Bleomycin is one twentieth of that used in the majority of chemotherapeutic regimens and thus the systemic side effects appear to be limited to nausea^{18, 90}. There has been two reported cases of post procedure lypothymia⁹⁰.

The most common local side effects reported by the majority of patients are pain (75%) and erythema limited to the tumor and surrounding treated tissue^{11, 45, 52, 66}. Most of the patients considered those symptoms tolerable as documented by the ESOPE study⁵². The

erythematous reaction usually recedes within a few days¹¹. Local tumor necrosis has been reported in 42% of cases⁶⁶. Delayed wound healing that may take several weeks or months to resolve, and epidermal erosions, and hematomas have been reported as rare events^{66,73,75}. The injection site reactions appear to be low (Type I and II) in the Wiebendirk toxicity scale⁹⁰.

Transient muscle spasms myoclonus, secondary to muscle stimulation by the electrical pulses, have been reported in 25% with lower intensity contractions in up to 78% of patients^{52,66}. Some authors advocate the administration of diazepam to alleviate these particular symptoms^{73,75}. Interestingly the majority of patients are willing to continue treatment if indicated, since the side effects are tolerable¹⁹.

11. What the future holds

Equipment evolution

Bioengineering developments and evolution of the technique continue to expand the applications of ECT as an alternative treatment for tumors that are inaccessible to current electrical probes. A redeveloped electroporator generator provides more flexibility to deliver the electric current at different phases of the cardiac cycle and the facility to connect several electrode probes around the tumor to deliver the electric pulses in synchrony. The other development is related to the type of electrodes. Longer array electrodes are now available to treat larger and deeper seated tumors, which in the past was a limitation of the procedure. These longer electrodes are insulated proximally to prevent short circuiting of current and to protect the normal tissues that are transgressed en-route to the tumor. These new devices have recently been applied clinically^{19, 102-103}. Kos et al. ¹⁰³ have proposed an algorithmic computer optimized analysis to treat deeper tumors, to minimize errors and to maximize treatment benefits.

Another novelty is the creation of finger applicators which allows the application of electrodes into lesions located in difficult to reach anatomic locations, such as the inside of the oral cavity. These finger electrodes have been already tested in the treatment of melanoma of the oral mucosa, and head and neck regions, with complete tumor regression ⁹⁰.

New endoluminal electrodes to reach internal lesions within the gastrointestinal tract have been used in animal models, as well as tumors transplanted into rabbit liver and murine models ^{87, 104-106}. These studies are encouraging and have demonstrated both *in vitro* and *in vivo* (human solid tumor masses in nude mouse models), that the use of flexible electrodes is safe, feasible and reproducible.

There is still the need to create harder needle probes for use in those difficult to treat subcutaneous and cutaneous tumors. These needles must be capable of penetrating into hard fibrotic tissue, while minimizing the bleeding risks and maintaining an adequate electrical distance between the probes.

Nanopulses

Higher amplitude electric pulses or “nanopulses” are currently being evaluated. The use of shorter pulse durations in the nanosecond range are believed to create smaller pores that allow ions but not large molecules to penetrate the membrane. These higher electric fields increase the possibility of producing non resealable pores, thus producing the effect of irreversible electroporation, and consequently allowing the cells to lose their cytoplasm with concomitant cell death. This principle is being used for tumor ablation, palliation or both ⁴³,

¹⁰⁷⁻¹⁰⁹. However in the treatment of melanoma, the advantages of these higher electric fields are not immediately evident.

ECT combination with Gene transfer, immunology and nanomolecules

Several studies suggest that the immune system is also involved in the mechanisms of response to ECT treatment and that this could be exploited for systemic disease control.

In a murine model ¹¹⁴, ECT followed by CpG oligonucleotide injection locally, produced an enhancement of the complete regression responses of tumors from 43 to 100 % , while also triggering systemic antitumor phenomenon with specific immune memory. Activation of dendritic cells released from the tumors are believed to be involved in this response with a recruitment of CD11c and CD11b receptors and an increase of TLR9 expression .

EP in combination with gene transfer is termed "Gene Electrotransfer ". It uses gene coding plasmids in order to transfer intracellularly a combination of genes, to either knock down the expression of a particular gene, or to stimulate temporary patterns of gene expression). The technique allows for avoidance of the biohazard issues intrinsic to viral vectors ^{101, 115-116}. Scientists at the Cork Cancer Research Center in Ireland have investigated in an *in vivo* murine model, the application of EP and local gene therapy for malignant tumors. A plasmid coding for two immunogenes, granulocyte-macrophage colony-stimulating factor (GM-CSF) and the B7-1 co-stimulatory immune molecule were delivered by EP. This resulted in the complete regression of the majority (60%) of non immunogenic tumors, while eliciting a tumour specific systemic response that hindered the metastatic growth in the liver in a 100 % of the mice. This was a durable potent response with tumor specificity. When the remaining non responders tumors were excised, an improved survival was observed when compared to the control groups, thus suggesting that the use of neoadjuvant electroporation and gene therapy given at an appropriate time interval prior to tumour excision or ablation could prevent the surfacing of metastatic disease ¹¹⁷⁻¹¹⁹. Regulatory T cell depletion at the time of electrogenetherapy stimulated improved complete response rates from 60 to near 100% suggesting a potential for improving efficacy of electroporation based immunogene therapy.

ECT with injection of TNF- α intra or peritumorally and suboptimal doses of Bleomycin in mice might have a positive immunomodulatory effect, and possibly adds a systemic component to the localized ECT treatment¹²⁰ . It has been noted that EP with INF- α used to treat Mycosis Fungoides (subcutaneous lymphoma) lesions produced a 100 % CR ¹²¹ The cytotoxic action of INF- α was attributed to its increased tumoral concentration and the prolonged time of action produced by the EP. ECT either with INF- α or TNF- α might permit the usage of less toxic doses, while enhancing clinical local and systemic immunological response rates and minimizing systemic side effects¹⁹.

ECT, radiotherapy and activation of bioreductive drugs

The "vascular lock" principle of EP has the potential to be used to "activate" bioreductive drugs such as Tirapazamine against neoplastic cells ⁴³, due to its vascular disrupting effect of tumor blood supply. In addition ECT has been shown to have a synergistic effect with radiotherapy in preclinical investigations, opening the possibility to use it as a radiosensitising tool for the palliation of subcutaneous lesion^{43, 122}.

The continued development of improved diagnostic methods will allow for earlier diagnosis of metastases, and possibly open the opportunities for *in situ* neoadjuvant treatment of

higher risk malignant melanomas by means of immunogene or cytokine therapies, hence establishing tumour specific responses which could prevent recurrence and eradicate disseminated micrometastases.

12. Summary

ECT with Bleomycin or Cisplatin is an effective treatment in the palliative management of unresectable recurrent cutaneous or subcutaneous melanoma metastases or in-transit disease, with OR rates of approximately 80-90%. ECT should now be considered as part of the armamentarium for treatment of loco regional advanced melanoma. The technology of ECT continues to evolve allowing for the treatment of metastatic lesions in other organs or anatomic regions. The principles of EP are already being applied in the clinical setting for the delivery of targeted therapies such as gene transfer and immunotherapy. These therapies along with ECT have the potential not only for local, but for distant treatment of tumors such as those of malignant melanoma, by stimulating a self-driven immune response to achieve systemic control of the disease.

However studies evaluating long term follow up results of ECT in melanoma are still needed prior to considering it as an option for curative intent. ECT has been proven to be an excellent palliative option in treatment of recurrent unresectable or in-transit disease.

13. References

- [1] Institute NC.
(<http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/HealthProfessional/>. Accessed 18 March 2011.
- [2] American Cancer Society: Cancer facts and figures 2010. 2010;
<http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-and-figures-2010>. Accessed 21 March, 2011.
- [3] American Cancer Society: Detailed Guide: Skin Cancer - Melanoma. What Are the Key Statistics About Melanoma? . 2009;
http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_melanoma_50.asp?sitearea=.
- [4] Hoekstra HJ. The European approach to in-transit melanoma lesions. *Int J Hyperthermia*. May 2008;24(3):227-237.
- [5] Yeatman TJ, Nicolson GL. Molecular basis of tumor progression: mechanisms of organ-specific tumor metastasis. *Semin Surg Oncol*. May-Jun 1993;9(3):256-263.
- [6] Glass LF, Fenske NA, Jaroszeski M, et al. Bleomycin-mediated electrochemotherapy of basal cell carcinoma. *J Am Acad Dermatol*. Jan 1996;34(1):82-86.
- [7] Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol*. Aug 15 2001;19(16):3635-3648.
- [8] Karakousis CP, Choe KJ, Holyoke ED. Biologic behavior and treatment of intransit metastasis of melanoma. *Surg Gynecol Obstet*. Jan 1980;150(1):29-32.
- [9] Ross MI, Balch CM. The current management of cutaneous melanoma. *Adv Surg*. 1991;24:139-200.
- [10] Meier F, Will S, Ellwanger U, et al. Metastatic pathways and time courses in the orderly progression of cutaneous melanoma. *Br J Dermatol*. Jul 2002;147(1):62-70.

- [11] Quaglino P, Mortera C, Osella-Abate S, et al. Electrochemotherapy with intravenous bleomycin in the local treatment of skin melanoma metastases. *Ann Surg Oncol*. Aug 2008;15(8):2215-2222.
- [12] Gimbel MI, Delman KA, Zager JS. Therapy for unresectable recurrent and in-transit extremity melanoma. *Cancer Control*. Jul 2008;15(3):225-232.
- [13] Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol*. Aug 15 2001;19(16):3622-3634.
- [14] Weinstock MA. Epidemiology and prognosis of anorectal melanoma. *Gastroenterology*. Jan 1993;104(1):174-178.
- [15] Garbe C, Buttner P, Bertz J, et al. Primary cutaneous melanoma. Prognostic classification of anatomic location. *Cancer*. May 15 1995;75(10):2492-2498.
- [16] Garbe C, Buttner P, Bertz J, et al. Primary cutaneous melanoma. Identification of prognostic groups and estimation of individual prognosis for 5093 patients. *Cancer*. May 15 1995;75(10):2484-2491.
- [17] Byrne CM, Thompson JF. Role of electrochemotherapy in the treatment of metastatic melanoma and other metastatic and primary skin tumors. *Expert Rev Anticancer Ther*. May 2006;6(5):671-678.
- [18] Sadadcharam M, Soden DM, O'Sullivan G C. Electrochemotherapy: an emerging cancer treatment. *Int J Hyperthermia*. May 2008;24(3):263-273.
- [19] Moller MG, Salwa S, Soden DM, O'Sullivan GC. Electrochemotherapy as an adjunct or alternative to other treatments for unresectable or in-transit melanoma. *Expert Rev Anticancer Ther*. Nov 2009;9(11):1611-1630.
- [20] Testori A, Rutkowski P, Marsden J, et al. Surgery and radiotherapy in the treatment of cutaneous melanoma. *Ann Oncol*. Aug 2009;20 Suppl 6:vi22-29.
- [21] Atkins MB, Hsu J, Lee S, et al. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*. Dec 10 2008;26(35):5748-5754.
- [22] Barranco SC, Romsdahl MM, Humphrey RM. The radiation response of human malignant melanoma cells grown in vitro. *Cancer Res*. Jun 1971;31(6):830-833.
- [23] Scala M, Gipponi M, Queirolo P, et al. Cryosurgery for advanced malignant melanoma of the facial skin. A case report. *In Vivo*. Jan-Feb 2006;20(1):153-156.
- [24] Hill S, Thomas JM. Use of the carbon dioxide laser to manage cutaneous metastases from malignant melanoma. *Br J Surg*. Apr 1996;83(4):509-512.
- [25] Kandamany N, Mahaffey P. Carbon dioxide laser ablation as first-line management of in-transit cutaneous malignant melanoma metastases. *Lasers Med Sci*. May 2009;24(3):411-414.
- [26] Hayes AJ, Clark MA, Harries M, Thomas JM. Management of in-transit metastases from cutaneous malignant melanoma. *Br J Surg*. Jun 2004;91(6):673-682.
- [27] Morton DL, Eilber FR, Holmes EC, et al. BCG immunotherapy of malignant melanoma: summary of a seven-year experience. *Ann Surg*. Oct 1974;180(4):635-643.
- [28] Rasmussen H, Rasmussen C, Lempicki M, et al. TNFerade Biologic: preclinical toxicology of a novel adenovector with a radiation-inducible promoter, carrying the human tumor necrosis factor alpha gene. *Cancer Gene Ther*. Nov 2002;9(11):951-957.

- [29] Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol*. Jul 1999;17(7):2105-2116.
- [30] Terando AM, Faries MB, Morton DL. Vaccine therapy for melanoma: current status and future directions. *Vaccine*. Sep 27 2007;25 Suppl 2:B4-16.
- [31] Yun CO, Nolan KF, Beecham EJ, Reisfeld RA, Junghans RP. Targeting of T lymphocytes to melanoma cells through chimeric anti-GD3 immunoglobulin T-cell receptors. *Neoplasia*. Sep-Oct 2000;2(5):449-459.
- [32] Lotem M, Machlenkin A, Hamburger T, et al. Autologous melanoma vaccine induces antitumor and self-reactive immune responses that affect patient survival and depend on MHC class II expression on vaccine cells. *Clin Cancer Res*. Aug 1 2009;15(15):4968-4977.
- [33] Gilboa E. DC-based cancer vaccines. *J Clin Invest*. May 2007;117(5):1195-1203.
- [34] Eggermont AM, Testori A, Marsden J, et al. Utility of adjuvant systemic therapy in melanoma. *Ann Oncol*. Aug 2009;20 Suppl 6:vi30-34.
- [35] Sondak VK, Flaherty LE. Adjuvant therapy of melanoma: is pegylated interferon alfa-2b what we've been waiting for? *Lancet*. Jul 12 2008;372(9633):89-90.
- [36] Schadendorf D, Algarra SM, Bastholt L, et al. Immunotherapy of distant metastatic disease. *Ann Oncol*. Aug 2009;20 Suppl 6:vi41-50.
- [37] Creech O, Jr., Kremenz ET, Ryan RF, Winblad JN. Chemotherapy of cancer: regional perfusion utilizing an extracorporeal circuit. *Ann Surg*. Oct 1958;148(4):616-632.
- [38] Smalley KS, Nathanson KL, Flaherty KT. Genetic subgrouping of melanoma reveals new opportunities for targeted therapy. *Cancer Res*. Apr 15 2009;69(8):3241-3244.
- [39] Mir LM, Glass LF, Sersa G, et al. Effective treatment of cutaneous and subcutaneous malignant tumours by electrochemotherapy. *Br J Cancer*. Jun 1998;77(12):2336-2342.
- [40] Ross MI. Surgery and other local-regional modalities for all stages of melanoma. *Curr Opin Oncol*. Mar 1994;6(2):197-203.
- [41] Moller MG, Lewis JM, Dessureault S, Zager JS. Toxicities associated with hyperthermic isolated limb perfusion and isolated limb infusion in the treatment of melanoma and sarcoma. *Int J Hyperthermia*. May 2008;24(3):275-289.
- [42] Eggermont AM, Gore M. Randomized adjuvant therapy trials in melanoma: surgical and systemic. *Semin Oncol*. Dec 2007;34(6):509-515.
- [43] Sersa G, Miklavcic D, Cemazar M, Rudolf Z, Pucihar G, Snoj M. Electrochemotherapy in treatment of tumours. *Eur J Surg Oncol*. Feb 2008;34(2):232-240.
- [44] Glass LF, Jaroszeski M, Gilbert R, Reintgen DS, Heller R. Intralesional bleomycin-mediated electrochemotherapy in 20 patients with basal cell carcinoma. *J Am Acad Dermatol*. Oct 1997;37(4):596-599.
- [45] Sersa G. The state-of-the-art of electrochemotherapy before the ESOPE study; advantages and clinical uses. *Eur J Cancer. Supplement*. 2006(4):8.
- [46] Mir LM. Bases and rationale of electrochemotherapy. *European Journal of Cancer. Supplement*. 2006;4:38-44.
- [47] Mir LM, Belehradek M, Domenge C, et al. [Electrochemotherapy, a new antitumor treatment: first clinical trial]. *C R Acad Sci III*. 1991;313(13):613-618.
- [48] Orlowski S, Belehradek J, Jr., Paoletti C, Mir LM. Transient electroporabilization of cells in culture. Increase of the cytotoxicity of anticancer drugs. *Biochem Pharmacol*. Dec 15 1988;37(24):4727-4733.

- [49] Larkin JO, Collins CG, Aarons S, et al. Electrochemotherapy: aspects of preclinical development and early clinical experience. *Ann Surg.* Mar 2007;245(3):469-479.
- [50] Weaver JC. Electroporation theory. Concepts and mechanisms. *Methods Mol Biol.* 1995;55:3-28.
- [51] Belehradec J, Jr., Orlowski S, Poddevin B, Paoletti C, Mir LM. Electrochemotherapy of spontaneous mammary tumours in mice. *Eur J Cancer.* 1991;27(1):73-76.
- [52] Marty M SG, Garbay JM, Gehl J, Collins CG, Snoj M, Billard V, Geertsen PF, Larkin JO, Miklavcic D, Paulovic I, Pavlin-Kosir SM, Cemazar M, Morsli N, Soden DM, Rudolf Z, Robert C, O'Sullivan GC, Mir LM. Electrochemotherapy -An easy, highly effective and safe treatment of cutaneous and subcutaneous metastases : Results of ESOPE (european standard operating procedures of electrochemotherapy) study. *European Journal of Cancer. Supplement.* 2006;4(11):3-13.
- [53] Sersa G, Cemazar M, Miklavcic D. Antitumor effectiveness of electrochemotherapy with cis-diamminedichloroplatinum(II) in mice. *Cancer Res.* Aug 1 1995;55(15):3450-3455.
- [54] Gehl J. Electroporation for drug and gene delivery in the clinic: doctors go electric. *Methods Mol Biol.* 2008;423:351-359.
- [55] Gehl J. Electroporation: theory and methods, perspectives for drug delivery, gene therapy and research. *Acta Physiol Scand.* Apr 2003;177(4):437-447.
- [56] Gehl J, Geertsen PF. Efficient palliation of haemorrhaging malignant melanoma skin metastases by electrochemotherapy. *Melanoma Res.* Dec 2000;10(6):585-589.
- [57] Snoj M, Cemazar M, Srnovrsnik T, Kosir SP, Sersa G. Limb sparing treatment of bleeding melanoma recurrence by electrochemotherapy. *Tumori.* May-Jun 2009;95(3):398-402.
- [58] Hofmann GA, Dev SB, Nanda GS, Rabussay D. Electroporation therapy of solid tumors. *Crit Rev Ther Drug Carrier Syst.* 1999;16(6):523-569.
- [59] Mir L, Gehl J, Sersa G, Collins CG, Garbay J, Billard V, Geertsen PF, Rudolf Z, OSullivan GC, Marty M. Standard operating procedures of hte electrochemotherapy: Instructions for the use of bleomycin and cisplastin administered either systemically or locally and electric pulses delivered by Cliniporator™ by means of ivansive or non-invasive electrodes. *European Journal of Cancer. Supplement.* 2006;4:14-25.
- [60] Testori A, Tosti G, Martinoli C, et al. Electrochemotherapy for cutaneous and subcutaneous tumor lesions: a novel therapeutic approach. *Dermatol Ther.* Nov 2010;23(6):651-661.
- [61] Sersa G CM, Rudolf Z. . Electrochemotherapy: advantages and drawbacks in treatment of cancer patients. *Cancer Therapy.* 2003;1:133-142.
- [62] Domenge C, Orlowski S, Luboinski B, et al. Antitumor electrochemotherapy: new advances in the clinical protocol. *Cancer.* Mar 1 1996;77(5):956-963.
- [63] Heller R, Jaroszeski M, Perrott R, Messina J, Gilbert R. Effective treatment of B16 melanoma by direct delivery of bleomycin using electrochemotherapy. *Melanoma Res.* Feb 1997;7(1):10-18.
- [64] Cemazar M, Milacic R, Miklavcic D, Dolzan V, Sersa G. Intratumoral cisplatin administration in electrochemotherapy: antitumor effectiveness, sequence dependence and platinum content. *Anticancer Drugs.* Jul 1998;9(6):525-530.
- [65] Mir LM, Banoun H, Paoletti C. Introduction of definite amounts of nonpermeant molecules into living cells after electroporomeabilization: direct access to the cytosol. *Exp Cell Res.* Mar 1988;175(1):15-25.

- [66] Gaudy C, Richard MA, Folchetti G, Bonerandi JJ, Grob JJ. Randomized controlled study of electrochemotherapy in the local treatment of skin metastases of melanoma. *J Cutan Med Surg*. May-Jun 2006;10(3):115-121.
- [67] Neumann E, Schaefer-Ridder M, Wang Y, Hofschneider PH. Gene transfer into mouse lyoma cells by electroporation in high electric fields. *EMBO J*. 1982;1(7):841-845.
- [68] Melvik JE, Pettersen EO, Gordon PB, Seglen PO. Increase in cis-dichlorodiammineplatinum (II) cytotoxicity upon reversible electroporabilization of the plasma membrane in cultured human NHIK 3025 cells. *Eur J Cancer Clin Oncol*. Dec 1986;22(12):1523-1530.
- [69] Okino M, Mohri H. Effects of a high-voltage electrical impulse and an anticancer drug on in vivo growing tumors. *Jpn J Cancer Res*. Dec 1987;78(12):1319-1321.
- [70] Belehradec M, Domenge C, Luboinski B, Orlowski S, Belehradec J, Jr., Mir LM. Electrochemotherapy, a new antitumor treatment. First clinical phase I-II trial. *Cancer*. Dec 15 1993;72(12):3694-3700.
- [71] Rudolf Z, Stabuc B, Cemazar M, Miklavcic F, Vodovnik L, Sersa G. Electrochemotherapy with bleomycin: the first clinical experience in malignant melanoma patients. *Radiol Oncol*. 1995(29):6.
- [72] Rols MP, Bachaud JM, Giraud P, Chevreau C, Roche H, Teissie J. Electrochemotherapy of cutaneous metastases in malignant melanoma. *Melanoma Res*. Oct 2000;10(5):468-474.
- [73] Heller R, Jaroszeski MJ, Glass LF, et al. Phase I/II trial for the treatment of cutaneous and subcutaneous tumors using electrochemotherapy. *Cancer*. Mar 1 1996;77(5):964-971.
- [74] Sersa G, Cufer T, Cemazar M, Rebersek M, Zvonimir R. Electrochemotherapy with bleomycin in the treatment of hypernephroma metastasis: case report and literature review. *Tumori*. Mar-Apr 2000;86(2):163-165.
- [75] Glass LF, Pepine ML, Fenske NA, Jaroszeski M, Reintgen DS, Heller R. Bleomycin-mediated electrochemotherapy of metastatic melanoma. *Arch Dermatol*. Nov 1996;132(11):1353-1357.
- [76] Heller R, Jaroszeski MJ, Reintgen DS, et al. Treatment of cutaneous and subcutaneous tumors with electrochemotherapy using intralesional bleomycin. *Cancer*. Jul 1 1998;83(1):148-157.
- [77] Rodriguez-Cuevas S, Barroso-Bravo S, Almanza-Estrada J, Cristobal-Martinez L, Gonzalez-Rodriguez E. Electrochemotherapy in primary and metastatic skin tumors: phase II trial using intralesional bleomycin. *Arch Med Res*. Jul-Aug 2001;32(4):273-276.
- [78] Byrne CM, Thompson JF, Johnston H, et al. Treatment of metastatic melanoma using electroporation therapy with bleomycin (electrochemotherapy). *Melanoma Res*. Feb 2005;15(1):45-51.
- [79] Kubota Y, Mir LM, Nakada T, Sasagawa I, Suzuki H, Aoyama N. Successful treatment of metastatic skin lesions with electrochemotherapy. *J Urol*. Oct 1998;160(4):1426.
- [80] Giraud P, Bachaud JM, Teissie J, Rols MP. Effects of electrochemotherapy on cutaneous metastases of human malignant melanoma. *Int J Radiat Oncol Biol Phys*. Dec 1 1996;36(5):1285.
- [81] Sersa G, Stabuc B, Cemazar M, Jancar B, Miklavcic D, Rudolf Z. Electrochemotherapy with cisplatin: potentiation of local cisplatin antitumour effectiveness by

- application of electric pulses in cancer patients. *Eur J Cancer*. Jul 1998;34(8):1213-1218.
- [82] Sersa G, Stabuc B, Cemazar M, Miklavcic D, Rudolf Z. Electrochemotherapy with cisplatin: clinical experience in malignant melanoma patients. *Clin Cancer Res*. Mar 2000;6(3):863-867.
- [83] Snoj M, Rudolf Z, Cemazar M, Jancar B, Sersa G. Successful sphincter-saving treatment of anorectal malignant melanoma with electrochemotherapy, local excision and adjuvant brachytherapy. *Anticancer Drugs*. Mar 2005;16(3):345-348.
- [84] Heller R. Treatment of cutaneous nodules using electrochemotherapy. *J Fla Med Assoc*. Feb 1995;82(2):147-150.
- [85] Kubota Y, Tomita Y, Tsukigi M, Kurachi H, Motoyama T, Mir LM. A case of perineal malignant melanoma successfully treated with electrochemotherapy. *Melanoma Res*. Apr 2005;15(2):133-134.
- [86] Sersa G, Stabuc B, Cemazar M, Miklavcic D, Rudolf Z. Electrochemotherapy with cisplatin: the systemic antitumour effectiveness of cisplatin can be potentiated locally by the application of electric pulses in the treatment of malignant melanoma skin metastases. *Melanoma Res*. Aug 2000;10(4):381-385.
- [87] Soden DM, Larkin JO, Collins CG, et al. Successful application of targeted electrochemotherapy using novel flexible electrodes and low dose bleomycin to solid tumours. *Cancer Lett*. Feb 8 2006;232(2):300-310.
- [88] Rabussay DP, Nanda GS, Goldfarb PM. Enhancing the effectiveness of drug-based cancer therapy by electroporation (electropermeabilization). *Technol Cancer Res Treat*. Feb 2002;1(1):71-82.
- [89] Tauceri F, Mura G, Roseano M, Framarini M, Ridolfi L, Verdecchia GM. Surgery and adjuvant therapies in the treatment of stage IV melanoma: our experience in 84 patients. *Langenbecks Arch Surg*. Mar 4 2008.
- [90] Campana LG, Mocellin S, Basso M, et al. Bleomycin-based electrochemotherapy: clinical outcome from a single institution's experience with 52 patients. *Ann Surg Oncol*. Jan 2009;16(1):191-199.
- [91] Landstrom FJ, Nilsson CO, Crafoord S, Reizenstein JA, Adamsson GB, Lofgren LA. Electroporation therapy of skin cancer in the head and neck area. *Dermatol Surg*. Aug 2010;36(8):1245-1250.
- [92] Landstrom FJ, Nilsson CO, Reizenstein JA, Nordqvist K, Adamsson GB, Lofgren AL. Electroporation therapy for T1 and T2 oral tongue cancer. *Acta Otolaryngol*. Dec 29 2010.
- [93] Sersa G, Cemazar M, Snoj M. Electrochemotherapy of tumours. *Curr Oncol*. Mar 2009;16(2):34-35.
- [94] Heller R, Gilbert R, Jaroszeski MJ. Clinical applications of electrochemotherapy. *Adv Drug Deliv Rev*. Jan 4 1999;35(1):119-129.
- [95] Snoj M, Cemazar M, Slekovec Kolar B, Sersa G. Effective treatment of multiple unresectable skin melanoma metastases by electrochemotherapy. *Croat Med J*. Jun 2007;48(3):391-395.
- [96] Snoj MR, Z. Paulin-Kosir, S. Cemanzar, M, Snoj, R. Sersa, G. . Long lasting complete response in melanoma treated by electrochemotherapy. *Eur J Cancer Suppl*. 2006;4(11):2.

- [97] Giardino R, Fini M, Bonazzi V, Cadossi R, Nicolini A, Carpi A. Electrochemotherapy a novel approach to the treatment of metastatic nodules on the skin and subcutaneous tissues. *Biomed Pharmacother*. Sep 2006;60(8):458-462.
- [98] Kaehler KC, Egberts F, Hauschild A. Electrochemotherapy in symptomatic melanoma skin metastases: intraindividual comparison with conventional surgery. *Dermatol Surg*. Jul 2010;36(7):1200-1202.
- [99] Heller LC, Heller R. Electroporation gene therapy preclinical and clinical trials for melanoma. *Curr Gene Ther*. Aug 2010;10(4):312-317.
- [100] Andersen MH, Gehl J, Reker S, et al. Dynamic changes of specific T cell responses to melanoma correlate with IL-2 administration. *Semin Cancer Biol*. Dec 2003;13(6):449-459.
- [101] Daud AI, DeConti RC, Andrews S, et al. Phase I trial of interleukin-12 plasmid electroporation in patients with metastatic melanoma. *J Clin Oncol*. Dec 2008;26(36):5896-5903.
- [102] Miklavcic D, Snoj M, Zupanic A, et al. Towards treatment planning and treatment of deep-seated solid tumors by electrochemotherapy. *Biomed Eng Online*. 2010;9:10.
- [103] Kos B, Zupanic A, Kotnik T, Snoj M, Sersa G, Miklavcic D. Robustness of treatment planning for electrochemotherapy of deep-seated tumors. *J Membr Biol*. Jul 2010;236(1):147-153.
- [104] Orlowski S, An D, Belehradek J, Jr., Mir LM. Antimetastatic effects of electrochemotherapy and of histoincompatible interleukin-2-secreting cells in the murine Lewis lung tumor. *Anticancer Drugs*. Jul 1998;9(6):551-556.
- [105] Ramirez LH, Orlowski S, An D, et al. Electrochemotherapy on liver tumours in rabbits. *Br J Cancer*. Jun 1998;77(12):2104-2111.
- [106] Soden D, Larkin J, Collins C, et al. The development of novel flexible electrode arrays for the electrochemotherapy of solid tumour tissue. (Potential for endoscopic treatment of inaccessible cancers). *Conf Proc IEEE Eng Med Biol Soc*. 2004;5:3547-3550.
- [107] Edd JF, Horowitz L, Davalos RV, Mir LM, Rubinsky B. In vivo results of a new focal tissue ablation technique: irreversible electroporation. *IEEE Trans Biomed Eng*. Jul 2006;53(7):1409-1415.
- [108] Nuccitelli R, Pliquett U, Chen X, et al. Nanosecond pulsed electric fields cause melanomas to self-destruct. *Biochem Biophys Res Commun*. May 5 2006;343(2):351-360.
- [109] Frey W, White JA, Price RO, et al. Plasma membrane voltage changes during nanosecond pulsed electric field exposure. *Biophys J*. May 15 2006;90(10):3608-3615.
- [110] Mir LM, Orlowski S, Belehradek J, Jr., Paoletti C. Electrochemotherapy potentiation of antitumour effect of bleomycin by local electric pulses. *Eur J Cancer*. 1991;27(1):68-72.
- [111] Mir LM, Orlowski S, Poddevin B, Belehradek J, Jr. Electrochemotherapy tumor treatment is improved by interleukin-2 stimulation of the host's defenses. *Eur Cytokine Netw*. May-Jun 1992;3(3):331-334.
- [112] Mir LM, Roth C, Orlowski S, et al. [Potentiation of the antitumoral effect of electrochemotherapy by immunotherapy with allogeneic cells producing interleukin 2]. *C R Acad Sci III*. 1992;314(12):539-544.
- [113] Heller L, Pottinger C, Jaroszeski MJ, Gilbert R, Heller R. In vivo electroporation of plasmids encoding GM-CSF or interleukin-2 into existing B16 melanomas

- combined with electrochemotherapy induces long-term antitumour immunity. *Melanoma Res.* Dec 2000;10(6):577-583.
- [114] Roux S, Bernat C, Al-Sakere B, et al. Tumor destruction using electrochemotherapy followed by CpG oligodeoxynucleotide injection induces distant tumor responses. *Cancer Immunol Immunother.* Sep 2008;57(9):1291-1300.
- [115] Heller LC, Heller R. In vivo electroporation for gene therapy. *Hum Gene Ther.* Sep 2006;17(9):890-897.
- [116] Cemazar M, Golzio M, Sersa G, Rols MP, Teissie J. Electrically-assisted nucleic acids delivery to tissues in vivo: where do we stand? *Curr Pharm Des.* 2006;12(29):3817-3825.
- [117] Cashman JP, Larkin JO, Casey G, et al. Immune gene therapy as a neoadjuvant to surgical excision to control metastatic cancers. *Cancer Lett.* Jan 5 2008.
- [118] Collins CG, Tangney M, Larkin JO, et al. Local gene therapy of solid tumors with GM-CSF and B7-1 eradicates both treated and distal tumors. *Cancer Gene Ther.* Dec 2006;13(12):1061-1071.
- [119] Tangney M, Casey G, Larkin JO, et al. Non-viral in vivo immune gene therapy of cancer: combined strategies for treatment of systemic disease. *Cancer Immunol Immunother.* Nov 2006;55(11):1443-1450.
- [120] Sersa G, Cemazar M, Menart V, Gaberc-Porekar V, Miklavcic D. Anti-tumor effectiveness of electrochemotherapy with bleomycin is increased by TNF-alpha on SA-1 tumors in mice. *Cancer Lett.* Jun 3 1997;116(1):85-92.
- [121] Peycheva E, Daskalov I, Tsoneva I. Electrochemotherapy of Mycosis fungoides by interferon-alpha. *Bioelectrochemistry.* May 2007;70(2):283-286.
- [122] Kranjc S, Cemazar M, Grosel A, Sentjurs M, Sersa G. Radiosensitising effect of electrochemotherapy with bleomycin in LPB sarcoma cells and tumors in mice. *BMC Cancer.* 2005;5:115.
- Websites:
- [201] American Cancer Society: Cancer Facts and Figures 2009. Atlanta, Ga: American Cancer Society, 2009. See a dermatologist. Skin cancer is very treatable when caught early. Also available online. 2009 [cited 2009 May 25, 2009]; Available from: http://www.cancer.org/docroot/PRO/content/PRO_1_1_Cancer_Statistics_2009_Presentation.asp
- [202] American Cancer Society: Detailed Guide: Skin Cancer - Melanoma. What Are the Key Statistics About Melanoma? 2009 May 14, 2009 [cited 2009 May 25]; Available from: http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_melanoma_50.asp?sitearea=
- [203] National Cancer Institute. Melanoma Treatment (PDQ)^R. Staging Information. 2009 [cited August 4, 2009.]; Available from: <http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/HealthProfessional/page4>
- [204] National Comprehensive Cancer Network. Melanoma 2009 [cited 2009 August 4, 2009.]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf

Treatment of Metastatic Melanoma

Edited by Ms Rachael Morton

ISBN 978-953-307-574-7

Hard cover, 348 pages

Publisher InTech

Published online 03, October, 2011

Published in print edition October, 2011

Surgery continues to be the mainstay treatment for melanoma localized to the primary tumor and/or lymph nodes. Results from randomized controlled trials indicate that sentinel node biopsy for the treatment of cutaneous melanoma of intermediate thickness has a beneficial effect on recurrence rates, and adjuvant radiotherapy to regional lymph node fields following surgical resection reduces loco-regional recurrence in patients at high risk of relapse. Isolated limb perfusion, electrochemotherapy, and photodynamic therapy continue to be evaluated for treatment of stage IV disease. However, the greatest excitement in new treatment has been with targeted therapies for genetic mutations. In particular, the promising results of partial and complete tumor response in stage IV disease from early phase trials of the B-RAF kinase inhibitors. This book provides a contemporary insight into the therapeutic treatment options for patients with metastatic melanoma and is relevant to clinicians and researchers worldwide. In addition, an update on current clinical trials for melanoma treatment has been included, and two chapters have been reserved to discuss the treatment of oral and uveal melanoma.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Mecker G. Möller, Slawomir Salwa, Declan M. Soden and Gerald C. O'Sullivan (2011). The Role of Electrochemotherapy in the Treatment of Malignant Melanoma, Treatment of Metastatic Melanoma, Ms Rachael Morton (Ed.), ISBN: 978-953-307-574-7, InTech, Available from:
<http://www.intechopen.com/books/treatment-of-metastatic-melanoma/the-role-of-electrochemotherapy-in-the-treatment-of-malignant-melanoma>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen