Electrochemotherapy for the treatment of melanoma skin metastases in the era of new drugs

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Summary

The incidence of melanoma has been increasing for more than 40 years and in the clinical course of this neoplasia cutaneous metastases are not unusual. Electrochemotherapy (ECT) is an already well recognized therapeutic tool for the local treatment of cutaneous and subcutaneous metastases of melanoma showing sustained anti-tumour activity and favourable toxicity profile. Treatment involves the local or intravenous administration of chemotherapeutic drugs followed by delivery of electrical pulses to the tumour.

Recent advances in systemic therapies have dramatically modified melanoma therapeutic approach on stage III and IV with increased survival rates. However, the cutaneous metastases management still represents a challenge for clinicians due to pain, bleeding, odour and psychosocial distress related to the lesions but also for the limited efficacy on the skin offered by newly available systemic strategies. ECT may be considered for local tumour control as an alternative to established local treatments but it could be also favourably associated to immune and target therapies to improve their efficacy. Recent findings suggest indeed that electrochemotherapy may exert a role in boosting anti-tumour immunity and to avoid skin metastases resistance to systemic treatments.

KEY WORDS: electrochemotherapy; melanoma skin metastases; immunotherapy; target therapy.

Introduction

The incidence of melanoma has been increasing for more than 40 years in western countries, although the incidence rate for all cancer sites combined is decreasing. Since 1975, age-standardized melanoma incidence in the United States nearly tripled to 22.9 per 100,000 persons in 2012 and also in Italy in the last 10 years melanoma diagnosis are almost doubled. Talking about prognosis, the 10-year survival rate for patients with an early-stage melanoma is greater than 95% but prognosis is much more severe for patients diagnosed with advanced disease: an overall 1-year survival of 25.5% and a median survival of 6.2 months were achieved, without any significant improvement during the last 30 years (1).

Melanoma accounts for about 18% of the total cases of cutaneous metastases (2) even if their management is often challenging. In fact, patients with cutaneous disease may suffer from pain, bleeding, and malodour determining a reduced quality of life. Since 2006, electrochemotherapy (ECT) has been introduced as a standardized procedure in the field of dermatology as a treatment option for cutaneous and subcutaneous lesions, including melanoma.

Electrochemotherapy

The first human trial conducted on 1991 demonstrated the efficacy and safety of electrochemotherapy in the treatment of cutaneous and subcutaneous metastases from different primary tumours. Then the field has rapidly developed since the procedure has been recognized as an effective and safe local treatment for cutaneous, subcutaneous and mucosal lesions (3, 4). A European project published in 2006 (ESOPE) established standardized operating procedures (5). The treatment can be administered in both outpatient or inpatient setting: in the first modality local anaesthesia and conscious sedation are preferable while if patient requires general anaesthesia it can be performed as a day hospital procedure. This loco-regional treatment is often scheduled as an inpatient procedure and most
commonly under general anaesthesia. Factors influencing the different anaesthesiology management of ECT are tumour site, disease burden, and patient choice.

After several studies investigating different cytotoxic agents, only two have been identified as the most suitable for ECT: bleomycin and cisplatin. Bleomycin determines mitotic cell death by a break in DNA, while cisplatin exerts an apoptotic effect on the cell. Electroporation increases the delivery of those cytotoxic agents through cell membrane enhancing their effects (more than 8000-fold for bleomycin and more than 80-fold for cisplatin) (5). Both the agents can be administered intratumorally or intravenously but Sersa et al. observed that the intratumoral administration of cisplatin is more effective than the intravenous one (4). For this reason, bleomycin at the standard dose of 15,000 IU/m² of body surface area is used intravenously and cisplatin (administered in a dose calculated based on tumour volume) is limited to intratumoural administration. In order to avoid the risk of lung toxicity, the maximum cumulative dose of bleomycin should not exceed 400,000 IU/m². The intratumoural route is more suitable in case of limited disease spread and in presence of less perfused tumour nodules, while the intravenous route is indicated in cases of disseminated disease or when tumour nodules are located in hard and fibrotic tissues.

The electroporation can be performed by a device approved for clinical use which delivers eight pulses of 100 µs at appropriate voltages with a real-time indirect control of electroporation. Electric pulses are currently applied to the lesion in a time window between 8 and 28 minutes after the intravenous injection of bleomycin or within 2 minutes after the intratumoural injection of drug (5). The electrodes most commonly used for treating cutaneous metastases are plate contact electrodes preferred in case of exophytic tumour nodules or needle electrodes (ranging from 1 to 3 cm in length) for deep seated lesions.

The treatment efficacy is principally based on electroporation. The electrodes deliver short electrical local pulses that lead to a destabilisation of the cell membrane and enhance the diffusion of cytostatic agents (bleomycin and cisplatin) inside tumour cells. Moreover, the consequent reduction of tumour blood flow and a localised vascular disruption increase drug effectiveness.

The procedure related pain is generally limited to the treated tumour and surrounding tissue and well-tolerated as more than 90% of patients would agree to undergo another treatment if indicated (2). ESOPE study underlined that patients treated with general anaesthesia reported significantly lower pain measured with a visual analogic scale than the patients treated in local anaesthesia (5).

A large series of data have demonstrated its clinical activity and tolerability, with response rates ranging up to 90% of treated lesions (6, 7) (Table 1). In a meta-analysis published on 2014 on more than 40 prospective studies five skin-directed therapies (ECT, radiation, photodynamic therapy, intralosomal therapy, and topical therapy) were compared. ECT demonstrated an OR rate of 75.4% with a low toxicity profile (grade 3 in less than 6% of patients). In this analysis, melanoma comprised 83.3% of all cutaneous metastases (8).

We already know multiple factors influencing treatment efficacy: coverage of deep margins, absence of visceral metastases, presence of lymphoedema, treatment of non-irradiated areas and tumour size <3 cm (9). These parameters help clinicians to decide whether a patient is more suitable for ECT alone or combined with other therapeutic strategies.

Melanoma new drugs: targeted therapies and check point inhibitors

Recent advances in systemic therapies have dramatically modified melanoma therapeutic approach with increased survival rates (Table 2). This uncovers the possibility that long-term disease control is achievable. Up to 57% of metastatic melanomas presents a BRAF mutation and responds positively to the selective BRAF inhibitors (BRAFi) vemurafenib and dabrafenib (10). Vemurafenib was the first BRAFi to be approved. Following phase 1 and 2 clinical trials which showed response rates of more than 50% in patients with metastatic melanoma, a randomised phase 3 trial was conducted (BRIM-3) comparing vemurafenib with dacarbazine in 675 patients with previously untreated, metastatic melanoma with the BRAF V600E mutation (11).

In an extended follow-up analysis of the total population and in the BRAF(V600E) and BRAF(V600K) mutation subgroups, the median overall survival was confirmed to be significantly longer in the vemurafenib group than in the dacarbazine group (13.6 vs 9.7 months), without differences between V600E and V600K (12). Similar results were obtained when comparing dacarbazine with the other BRAFi dabrafenib. In the BREAK-3 trial, 250 were randomly assigned to receive either dabrafenib (187 patients) or dacarbazine (63 patients). Median progression-free survival was 5.1 months for dabrafenib and 2.7 months for dacarbazine, with a confirmed striking advantage for dabrafenib also in terms of response rates (50 vs 6%) (10).

Various resistance mechanisms lead to a MAPK pathway reactivation with a dramatic disease progression in approximately 50% of patients within 6 to 7 months from the start of target therapy (13). More recently, MEK inhibitors (MEKi), such as cobimetinib and trametinib have also been associated to BRAFi improving progression-free and overall survival in BRAF and NRAS mutant melanomas. To date, the combination regimens represent the standard for targeted therapies. In phase 1 and 2 studies, combination regimens showed improved progression-free survival over single inhibitor therapy. In the Combi-D study, 423 BRAF mutant patients were randomly assigned to receive dabrafenib and trametinib (n=211) or dabrafenib only (n=212). Median over-
Electrochemotherapy for the treatment of melanoma skin metastases in the era of new drugs

75

...versus 18.7 months in the dabrafenib only group with a median progression-free survival of 11 and 8.8 months respectively (22). Similarly, in the Combi-V study, 704 patients with metastatic melanoma with a BRAF V600 mutation were randomised to receive either a combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) or vemurafenib (960 mg twice daily) (23). Median progression-free survival was 11.4 months in the combination-therapy group and 7.3 months in the vemurafenib group. The objective response rate was 64% in the combination-therapy group and 51% in the vemurafenib group. Also the combination of vemurafenib and cobimetinib was proven to be superior to vemurafenib alone in a phase 3 randomised clinical trial including 495 patients with previously untreated unresectable locally advanced or metastatic BRAF V600 mutation-positive melanoma. The combination showed a significantly higher clinical activity in terms of response rates (68 vs 45%), progression-free survival (median: 9.9 vs 6.2 months) and survival (9 months overall survival 81 vs 73%) (24).

The percentages of best confirmed response is 69% in the Combi-D trial, 64% in the Combi-V and 69.6% in the co-BRIM trial. Most important, the landmark analysis confirmed a long term benefit on overall survival, with 3 years survival rates of 44% in the Combi-D, 45% in the Combi-V and 37.4% in the co-BRIM. The study of immunoregulatory mechanisms has led to the development of a new therapeutic approach on advanced melanomas. The first agent developed in this class, the anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody ipilimumab, received regulatory approval for the treatment of advanced melanoma in 2011. In a recent pooled analysis of overall survival, a three years rate of 22% was obtained in both previously treated and untreated patients (25). The most common side effects of this drug consist of immune-mediated reactions (irAEs) developing more frequently in the skin, gastro-intestinal tract (mainly diarrhoea),

<table>
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<th>Drug</th>
<th>RR (%)</th>
<th>CR (%)</th>
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<td>Ipilimumab</td>
<td>4.2 – 19%</td>
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<td>Pembrolizumab</td>
<td>38 – 46%</td>
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<td>Dabrafenib</td>
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<td>Vemurafenib</td>
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<td>4 – 8%</td>
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<tr>
<td>Dabrafenib + Trametinib</td>
<td>64 – 67%</td>
<td>11 – 13%</td>
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<td>Vemurafenib + Cobimetinib</td>
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liver and endocrinial glands. The first randomized phase II study comparing different dose regimens in metastatic melanoma (0.3, 3 or 10 mg/kg IV every 3 weeks), showed that both 3 and 10 mg/kg induced promising response, even if the latter dose was interested by an increase in immune related adverse events (26). In a phase III trial, ipilimumab ± glycoprotein 100 peptide (gp100) vaccine was compared with gp100 vaccine alone in patients with unresectable stage III or stage IV melanoma. Ipilimumab significantly improved median overall survival (OS) compared with gp100 vaccine monotherapy (10.1 months vs 6.4 months) (27). In another randomized phase III trial, the combination of ipilimumab (10 mg/kg) and dacarbazine (850 mg/sqm) resulted in significantly superior OS compared to dacarbazine (850 mg/sqm) plus placebo (11.2 months vs 9.1 months) (28).

Noteworthy, ipilimumab produced a plateau in survival curves: a recent pooled analysis of OS data for 1.861 patients enrolled in 10 prospective and 2 retrospective trials, with up to 10 years follow-up, showed that the survival curve began to plateau around 3 years after treatment. Three-year OS rates were 22, 26, and 20% for all, treatment-naive, and previously treated patients, respectively (25). New immunoregulatory drugs, the antibodies blocking the programmed death-1 (PD-1) pathway, pembrolizumab and nivolumab, achieved higher response rates with less side effects compared to ipilimumab alone (29). A randomized phase III study comparing nivolumab vs dacarbazine in previously untreated melanoma without BRAF mutation demonstrated superior overall response rate (ORR, 40 vs 13.9%, respectively) and increased 1-year OS (72.9 vs 42.1%, respectively). Moreover, nivolumab treatment-related adverse events occurred in 11.7% of the patients receiving nivolumab and 17.6% of the patients receiving dacarbazine, respectively (30). In CheckMate 037 phase III trial, patients were randomly assigned 2:1 to receive nivolumab 3 mg/kg every 2 weeks or investigators’ choice chemotherapy until progression or unacceptable toxic effects. At first interim analysis on 120 and 47 randomized patients, confirmed objective responses were reported in 31.7% of patients in the nivolumab group vs 10.6% of patients in the chemotherapy group (31). The activity of pembrolizumab for advanced melanoma was firstly shown in 2013 by a phase IB study achieving an ORR of 38% in both ipilimumab pre-treated or not pre-treated patients (32). In the Keynote-002 randomized phase II clinical trial, two different doses of pembrolizumab (2 mg/kg and 10 mg/kg) were then implied and compared with chemotherapy. At enrolment, patients had progressive disease after ipilimumab or, if BRAF mutated, after BRAF or MEK inhibitors, or both. Results showed an improvement in progression-free survival (PFS) at 6 months for both doses, with slight prevalence for pembrolizumab 2 mg/kg (33). Pembrolizumab was then also compared to ipilimumab. In a large randomized phase III study, 834 patients with advanced melanoma were treated either with pembrolizumab at a dose of 10 mg/kg every 2 or every 3 weeks or with 4 doses of ipilimumab (3 mg/kg every 3 weeks). Results were largely better for pembrolizumab both for 6-months PFS rates (47.3-46.4-26.5%) and response rates (74.1-68.4-58.2%). There were no significant differences for both pembrolizumab every 2 and every 3 weeks (29).

A dual checkpoint blockade with concurrent ipilimumab and nivolumab resulted more effective than either agent alone (34). In a phase II clinical trial (CheckMate 069), 2-year overall survival was 63.8% for those patients assigned to nivolumab plus ipilimumab and 53.6 for those assigned to ipilimumab alone (35). Among patients with BRAF wild-type melanoma, the rate of confirmed objective response was 61% (44 of 72 patients) in the group that received both ipilimumab and nivolumab versus 11% (4 of 37 patients) in the group that received ipilimumab alone (36). In another clinical trial Larkin et al. demonstrate that median progression-free survival was 11.5 months with nivolumab plus ipilimumab, as compared with 2.9 months with ipilimumab, and 6.9 months with nivolumab. In patients with tumours positive for the PD-1 ligand (PD-L1), the median progression-free survival was 14.0 months in the nivolumab-plus-ipilimumab group and in the nivolumab group, but in patients with PD-L1-negative tumours, progression-free survival was longer with the combination therapy than with nivolumab alone (11.2 months vs 5.3 months) (34).

Discussion

**Electrochemotherapy versus new drugs or electrochemotherapy and new drugs?**

To date, the main indication for ECT alone is in patients with loco-regional metastases i.e. with stage IIIc melanoma, whilst in stage IV the frequent onset of rapidly developing visceral metastases in association with skin localisations requires mostly a systemic approach. On the other side ECT treatment could be a preferable option in many melanoma patients with advanced age and with comorbidities when systemic therapy may not be considered. In those situations, ECT can be taken in account thanks to its simplicity, cost-effectiveness, safety and limited toxicity (37). Furthermore, despite the new systemic drugs (immune or target therapy) have changed the management of advanced melanoma, most patients require a high number of lines of therapy with the risk of depletion of therapeutic options in case of non-responders or progressing disease. So, ECT could be favourably combined with new systemic drugs in order to prolong survival, to increase local response in the skin or induce responses in refractory sites.

In a first report concerning the ECT-BRAFi association, the procedure was performed during dabrafenib treatment and proved to be a safe and valuable option in a challenging patient who developed tumour resis-
Electrochemotherapy for the treatment of melanoma skin metastases in the era of new drugs

In conclusion, systemic therapy alone often has limited efficacy in cutaneous metastases while ECT offers a high OR rate. So, despite the revolution caused by immune and target strategies, ECT maintains an important role. In particular, it could be taken in account as monotherapy for local disease control in a palliative setting or in case of patient's comorbidities contraindicating a systemic approach. Moreover, it could be used in association with the new drugs to improve drug efficacy or to avoid skin metastases resistance emerging during a systemic treatment.

Conflict of interest
Authors state no conflict of interest.

References


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