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The use of electrochemotherapy in treating superficial melanoma metastases

Relevance. *Electrochemotherapy (ECT) is a novel modality for treatment of skin, cutaneous, or subcutaneous malignant tumours.*

Purpose of the study – to study the effectiveness of ECT for treatment of superficial metastases of melanoma.

Methods and materials. 4 patients with stage IV skin melanoma received ECT in the Center of bones, Soft Tissue Tumours and Melanoma of the Kazakh Institute of Oncology and Radiology (KazIOR). ECT was made using CliniporatorTM (IGEA, SpA, Italy) and hexagonal needle electrodes inserted subcutaneously directly into deep tumour tissues and surrounding areas. Electric pulses were administered during 8 minutes after intravenous injection of 15 mg / m² of bleomycin. ECT was performed according to the European Standard Operating Procedures of Electrochemotherapy (ESCOPE).

Results. All patients had a complete response (CR) of tumour nodes 15-30 days after ECT. 2 patients had no recurrence and growth of new lesions 10 months after ECT. One patient had tumour recurrence 3 months after ECT, and one – 5 months after ECT.

Conclusion. ECT can be a method of choice in treating patients with superficial melanoma metastases. ECT increases the effectiveness of systemic and local therapy.

Keywords: metastatic melanoma, electrochemotherapy, bleomycin, superficial skin melanoma.

Introduction. Since 1973, worldwide incidence of melanoma has increased by 200% [1]. The same trend is observed in Kazakhstan. In 5 years, 2011 to 2015, the morbidity has increased by 25%. 330 patients in average were newly diagnosed with melanoma in Kazakhstan yearly. The total number of registered patients with that diagnosis has amounted to 2238 in 2015. Despite the fact that the patients with stage IV have accounted for only 8%, the 5-year survival has remained rather low – 58.5% [2].

Melanoma is one of the most malignant tumours. Melanoma is characterized by rapid metastasis into vital organs and systems. The risk of its recurrence and progression depends on the primary stage of the disease. 5-year survival in local-regional stages differs from 97% at IA to 40% at IIIC stage. In the metastatic process, 5-year survival depends on the localization of metastases: 62% in case of metastatic lesions and lymphatic lymph node involvement; the involvement of lungs reduces 5-year survival to 53%; and the involvement of other visceral organs results in a decrease to 33 % [3].

Despite a relatively favourable prognosis for superficial metastases, the treatment of this category of patients remains one of the most complex and urgent. The presence of skin recurrences and metastases worsens the quality of life of patients due to the presence of a visible tumour, severe pain syndrome, the need for regular surgical dressings, and the development of inflammatory and infectious complications.

The existing methods of treatment of patients with skin metastases – from systemic therapy, surgery, radiotherapy to local-regional chemotherapy – are not efficient enough [4, 5]. The possibility for targeted therapy is limited to a group of patients with a proven mutation of BRAF gene. In this regard, the search for new, most efficient methods of treatment of this category of patients remains relevant.

To date, the effectiveness of this method was demonstrated in multiple studies [6-8]. According to the obtained results, an objective response was observed in 80 patients (94%) one month after the first ECT. Partial response (PR)

was achieved in 39 patients (48%), with a complete response (CR) in 19 patients (24%) after the reinitiation of treatment. 19 out of 41 patients (48%) with CR after the first ECT underwent a second cycle because of the new lesions after a median of 6 months. During a follow-up of an average of 26 months, 6 patients had local recurrence, with a 2-year local progression-free survival rate of 87%. Advantages of the method: the time of treatment is less than 30 minutes; repeated sessions are possible; minimal side effects; and the possibility of combination with other methods of treatment [6]. ECT remains an effective method of palliative treatment of superficial metastases [9].

The clinical studies have revealed the following side effects of ECT technique:

- Local pain syndrome at the site of application of the electrode
- Nausea
- Vomiting
- Slightly expressed itching, erythema, peeling of the skin in the area of exposure passing without treatment.
- Permanent hyperpigmentation of skin in the area of cytostatic administration. The highest risk of hyperpigmentation – with bleomycin.
- Moderate aseptic inflammation of skin surrounding the tumour during treatment [10, 11].

In Kazakhstan, electrochemistry was first applied in the Center for Bone, Soft Tissue Tumours and Melanoma of the Kazakh Institute of Oncology and Radiology (KazIOR) in December 2016. The first experience of using this technique is presented in this study.

Purpose of the study – to study the effectiveness of electrochemical method of treatment of superficial metastases of melanoma.

Methods and materials. 4 patients with stage IV melanoma selected for ECT treatment met the following criteria: satisfactory general status, ECOG <2, inoperable multiple superficial melanoma metastases. Those patients have refused standard chemotherapy and were not subject to targeted therapy.

ECT contraindications taken into account during patient selection: confirmed allergy to bleomycin; pulmonary, cardiac, renal and hepatic insufficiency; probable life expectancy not more than 3 months; brain metastases; progressive metastases in internal organs; an installed pacemaker, insulin pump or electronic implants; impaired blood clotting; epilepsy; pregnancy or breastfeeding; acute infections including acute skin inflammation.

ECT procedure: all the patients received i/v bolus of Bleomycin at the rate of 15 mg / m² during 8 minutes. Then electrical impulses were applied to each tumour site and adjacent tissues at a distance of 15-20 mm. The electric currents were supplied with a needle electrode 2-3 cm long based on the size of the source. The electrodes were attached to a high-voltage impulse generator Cliniporator™ (IGEA, SpA, Italy). The voltage up to 1000V was supplied as a compressed circuit of eight pulses at the frequency of 5000Hz. The voltage and current supplied to each tumour node were software regulated. Maximum duration of the procedure – 30 minutes. Each patient received one treatment session. The method of anaesthesia was determined depending on the anatomical location of the tumour. In the event of pain syndrome after the procedure the patients received analgesic therapy with standard NSAIDs. No other side effects except pain syndrome stopped by NSAIDs were observed during our first application of ECT.

The efficiency of ECT was determined by comparing the size of metastatic lesion before and after treatment, the number of lesions, the presence of M1b-c metastases, the relapses and the appearance of new metastatic lesion during 8 months after treatment.

Results. One of the peculiarities of the method was that the treatment effect was evident already 20 days after the procedure and remained in force for a different period without additional treatment. All patients had a complete response of cutaneous metastases to treatment after 20 days. In 2 patients with pulmonary metastases, there was no growth of the metastases. 2 patients who had skin tumour nodes 5-30 mm and 5-40 mm before treatment had a relapse after 3 and 5 months, respectively. 2 other patients had no skin metastases throughout the follow-up period of 10 months.

Summarized results of treatment:

- CR of tumour nodes was observed in all patients 15-30 days after ECT.
- 2 patients had no recurrence and growth of new lesion within 10 months from the date of ECT.
- 1 patient had a tumour recurrence 3 months after ECT.
- 1 patient had a relapse of metastatic formations and the appearance of new lesions in nearby anatomical areas 5 months after ECT (Table 1).

Table 1 – Evaluation of ECT efficiency in patients with skin metastases of melanoma

Clinical cases	1	2	3	4
Sizes of metastatic lesions before treatment	5-20mm	10-50mm	5-40mm	5-30mm
Number of lesions before treatment	20	5	6	25
Size and number of metastatic lesions after treatment	No lesions			
Presence of M1b-c metastases before treatment	Multiple lesions in the lungs	No	No	Multiple lesions in the lungs
Presence of M1b-c metastases after treatment	Multiple lesions in the lungs (stable CT picture)	No	The appearance of metastatic lesions of the lungs 6 months after treatment	Multiple lesions in the lungs (stable CT picture)
Time before relapse and the appearance of new local metastatic lesions after treatment (months)	No	No	6 months	3 months

Clinical case №1. Patient B., 38years old. Back skin melanoma St IV (T3bN1M1b). Condition: after surgery, 8 courses of chemotherapy (3 lines of chemotherapy). Stabilization of lung metastases. Progression: metastatic lesion of the back skin.

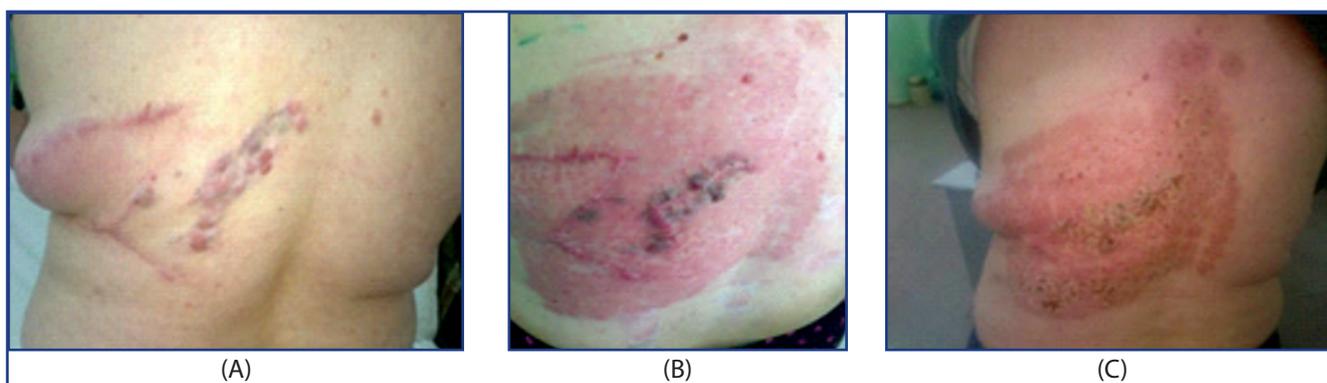


Figure 1 – Patient B. 38years old. Back skin melanoma St IV (T3bN1M1b): (A) Before treatment; (B) 20 days after treatment; (C) 5 months after treatment

20-30 days after treatment, CR of metastatic lesions was determined by visual examination and palpation. There was no progression of metastatic lesions of the back skin within 10 months. The stabilization of metastases in the lungs was confirmed by computed tomogra-

phy (CT) (Table 1).

Clinical case №2. Patient D., 58years old. Melanoma of the left leg skin St IV (T4bN1M1a). Condition: after surgery (wide excision of the left leg skin tumour + Duchene's operation on the left leg).

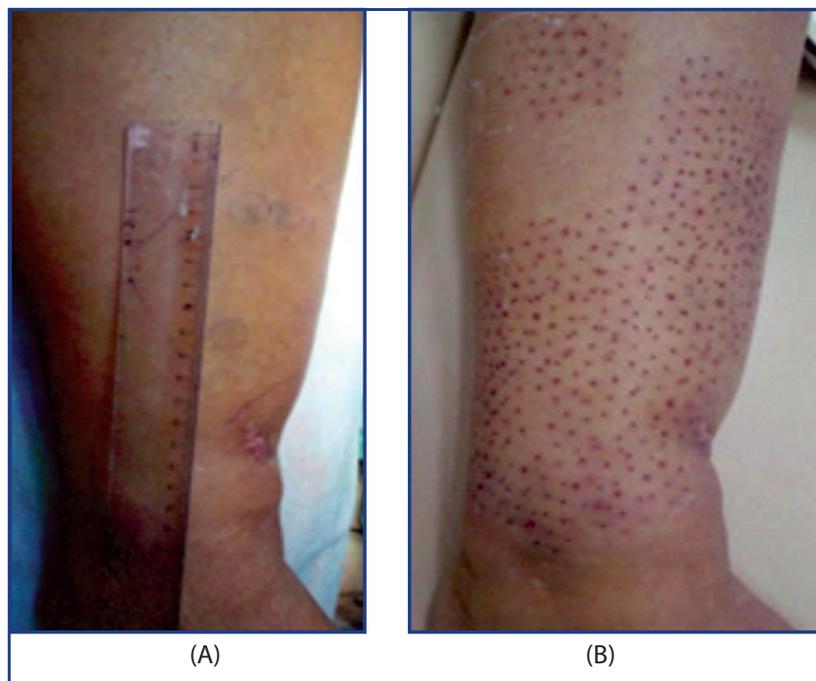


Figure 2 – Figure 2 - Patient D., 58years old. Melanoma of the left leg skin St IV (T4bN1M1a): (A) Before treatment, (B) 15 days after treatment

15-20 days after treatment, the resorption of metastatic foci was determined by visual examination and palpation. There was no local recurrence of melanoma metastasis within 10 months. The absence of distant haematogenous and lym-

phogenous metastases was confirmed by CT and MRI (Table 1).

Clinical case №3. Patient I., 78years old. Metastasis of melanoma to the right leg skin without primary-identified lesion StIV(TxN0M1a).

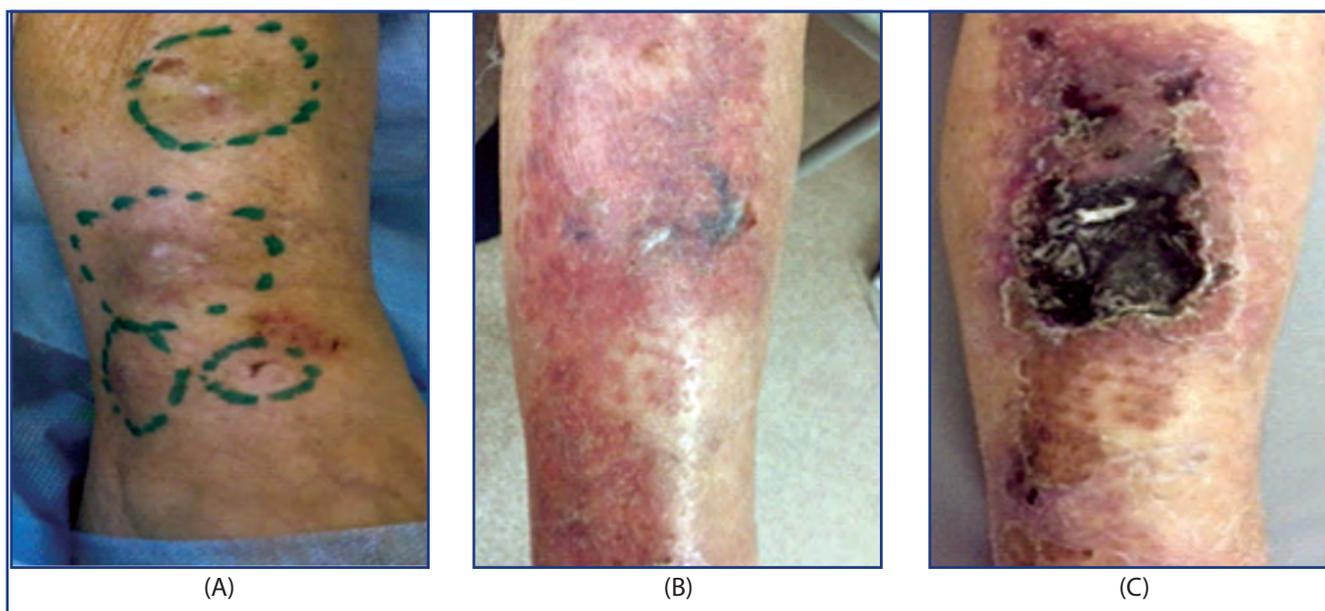


Figure 3 – Patient I., 78years old. Metastasis of melanoma to the right leg skin without primary-identified lesion StIV(TxN0M1a): (A) Before treatment, (B) 30 days after treatment, (C) Complete necrosis of tumour nodes after 3 months.

25 and 30 days after treatment, the resorption of metastatic lesions was confirmed by visual examination, palpation and ultrasonography. Six months after ECT the disease progressed as the new metastatic lesions appeared in soft tissues, on the left leg skin and in the lungs, as evi-

denced by local examination and CT (Table 1).

Clinical case №4. Patient A., 68 years old. Skin melanoma of the left inguinal area with a metastatic lesion of inguinal lymph nodes, lung, and soft tissues of the anterior thoracic wall. St IV (T4vN1M1b).

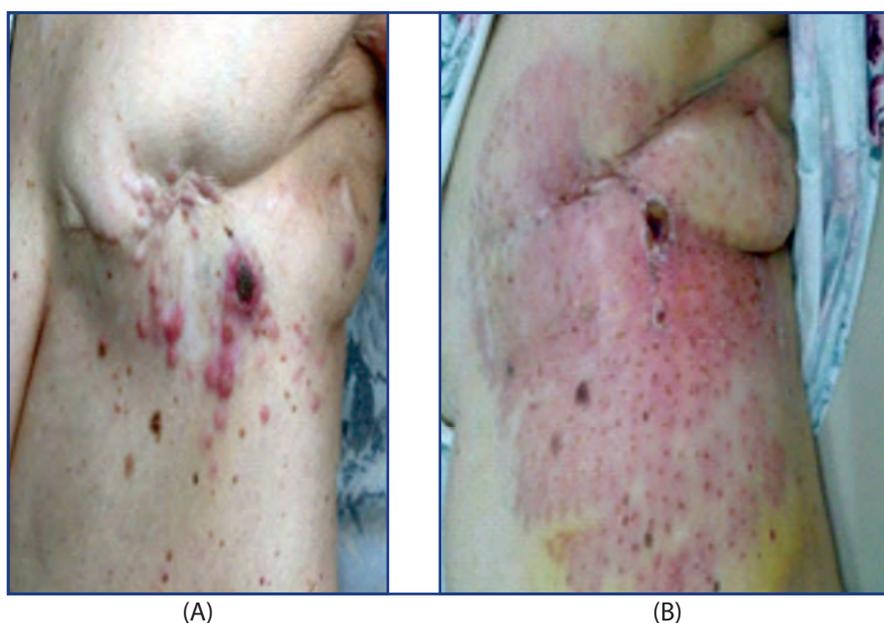


Figure 4 – Patient A., 68 years old. Skin melanoma of the left inguinal area with a metastatic lesion of inguinal lymph nodes, lung, and soft tissues of the anterior thoracic wall. St IV (T4vN1M1b): (A) Before treatment, (B) 20 days after treatment.

20 days after treatment, the resorption of metastatic lesions was confirmed by visual examination, palpation and ultrasonography. 3 months after ECT, the disease progressed as the new metastatic lesions appeared in soft tissues, on the skin of the anterior chest wall, and the metastatic lesions in the lungs have progressed as evidenced by local examination and CT (Table 1).

Conclusion. Our first experience with ECT has shown the possibility of using this method in treating melanoma skin metastases. ECT can be a method of choice for treating superficial melanoma metastases of different localities with a high risk of local recurrence and further dissemination of the tumour.

ECT provides good results with minimal side effects and allows improving the quality of life of patients.

Further study involving more patients and a longer monitoring of the treated patients are required to completely evaluate the efficiency of this method of treatment.

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