

Effective Treatment of Multiple Unresectable Skin Melanoma Metastases by Electrochemotherapy

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Multiple unresectable melanoma skin metastases pose a treatment problem, especially in centers where isolated limb perfusion is not available. We report the case of a 59-year-old woman who developed multiple small unresectable cutaneous melanoma metastases on the thigh after her lower limb was amputated. Electrochemotherapy with bleomycin resulted in good local control of the disease, with a complete response of the treated melanoma nodules (224 tumor nodules) after 4 treatment sessions. Comparison between electrochemotherapy using repetition frequency of the applied electric pulses of 1 Hz and 5 kHz demonstrated equal antitumor effectiveness. Electrochemotherapy with intravenous bleomycin can also be used as a treatment of choice for local control of multiple unresectable cutaneous melanoma skin metastases.

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Multiple melanoma cutaneous metastases are currently treated by local tumor surgery, isolated limb perfusion, and isolated limb infusion or irradiation (1-3). These approaches often fail, so the search for new palliative approaches is under way.

Several clinical studies have already demonstrated the clinical benefit of electrochemotherapy in general, as well as in the treatment of single or multiple cutaneous melanoma nodules (4-10). A recent report of the European Standard Operating Procedures on Electrochemotherapy (ESOPE study) demonstrated the anti-tumor effectiveness of electrochemotherapy, with 85% objective responses in treated nodules of various malignancies (4). Electrochemotherapy, a treatment that combines electroporation of a tumor with systemic or local administration of bleomycin or cisplatin, has been proved to provide long-lasting tumor control of

the treated nodules with minimal side effects and good cosmetic results. The principal mechanism of electrochemotherapy is the increased plasma membrane permeability due to the electroporation of cells in tumors, which increases drug effectiveness by enabling the drug to reach its intracellular targets (11). Currently, electrochemotherapy is limited to the treatment of cutaneous and subcutaneous tumor nodules. The major drawback of this method is the pain associated with the application of electric pulses (8,11).

In most cases, between 10 and 22 tumor nodules were treated by electrochemotherapy, and in the instance of treatment failure or growth of new metastases, the treatment was repeated with equal treatment effectiveness (5,6). To date, the only reported successful repetitive treatment by electrochemotherapy of multiple unresectable tumor nodules concerned Kaposi sarcoma (12). So far, no cases with multiple unresectable cutaneous melanoma nodules treated by electrochemotherapy have been reported. It has been demonstrated that the therapeutic window for the application of electric pulses to tumor nodules is 8 to 28 minutes after intravenous injection of bleomycin (13). In the case of multiple metastases, this time limit constitutes a substantial constraint, since when using a 1 Hz repetition frequency, each electric pulse application lasts at least 10 seconds. One newly designed electric pulse generator enables repetition frequency of the applied electric pulses up to 5 kHz. This allows rapid treatment with a treatment capacity of up to 100 nodules in each treatment session (14).

We report the case of a woman with multiple small unresectable cutaneous melanoma metastases (224 nodules) that were treated by electrochemotherapy in 4 treatment sessions. Furthermore, during the first electrochemotherapy session we performed a comparison between electrochemotherapy using repetition frequency of the applied electric pulses of 1 Hz and 5 kHz and demonstrated equal effectiveness of both.

Case report

A 59-year-old woman was referred to the Institute of Oncology Ljubljana in September 2003 after a melanoma of Breslow thickness of 2 mm (15) was removed from her left calf. Re-excision and sentinel lymph node biopsy were performed, and one out of three sentinel lymph nodes was positive. Chest x-ray and abdominal ultrasound did not show any signs of metastases. Deep inguinal dissection was performed and in eight lymph nodes no metastatic deposits were found. In January 2004, multiple cutaneous metastases emerged on the calf and were treated by irradiation with a total dose of 36 Gy given at 6 Gy daily fractions, 2 fractions per week. Soon, multiple metastases appeared on the thigh and were irradiated with a total dose of 24 Gy given at 8 Gy weekly fractions for three weeks. In June 2004, a partial regression of numerous metastases was noted. On the calf, ulceration of metastases was also noted. It spread all over the lateral part of the calf and became infected. Therefore a below-knee amputation was performed and the remaining multiple unresectable metastases in the thigh posed a treatment problem, especially because isolated limb perfusion is not available at our center. With the patient's consent, we decided to treat the multiple melanoma nodules by electrochemotherapy.

Electrochemotherapy was performed under general anesthesia as described in detail in standard operating procedures (13). Bleomycin (Pharmachemie, Harlem, Netherlands) was given intravenously (15 000 IU/m²) in bolus lasting 30-45 seconds. Electric pulses were applied to the tumor nodules with a Cliniporator (IGEA srl., Carpi, Italy) in the time window between 8 and 28 minutes after the injection of the drug. Plate electrodes with a 6 mm gap between them were used. Electrical parameters were the following: 8 electric pulses of 1300 V/cm amplitude over distance and duration of 100 μ s. Two different electric pulse rep-

etition frequencies were separately applied – 1 Hz and 5 kHz, and there could be no interference of the frequencies.

Four consecutive electrochemotherapy sessions were performed on multiple unresectable cutaneous melanoma nodules on the thigh. In the first session in February 2006, the metastases were treated with electrochemotherapy using electric pulse repetition frequencies of 1 Hz and 5 kHz. The left part of the thigh (11 tumor nodules) was treated with 1 Hz and the right part (31 tumor nodules) with 5 kHz repetition frequency (Figure 1A). After treatment, the treated nodules started to flatten out and within 5 weeks regressed completely, but the skin remained pigmented in some places. On the remaining mela-

noma nodules, another three electrochemotherapy sessions were performed (April, July, and October 2006), using only 5 kHz repetition frequency of the applied electric pulses, as no difference in tumor response was observed with regard to the frequency of electric pulses applied (Figure 1B). Altogether 182 nodules were treated in the last three sessions.

At the end of the observation period (November 2006, nine months after the first session) good local tumor control was observed in the treated area. Moreover, even nodules that were not treated did not progress (Figure 1B, 1C, 1D). In November 2006, systemic spread of the disease was established and the patient started chemotherapy.

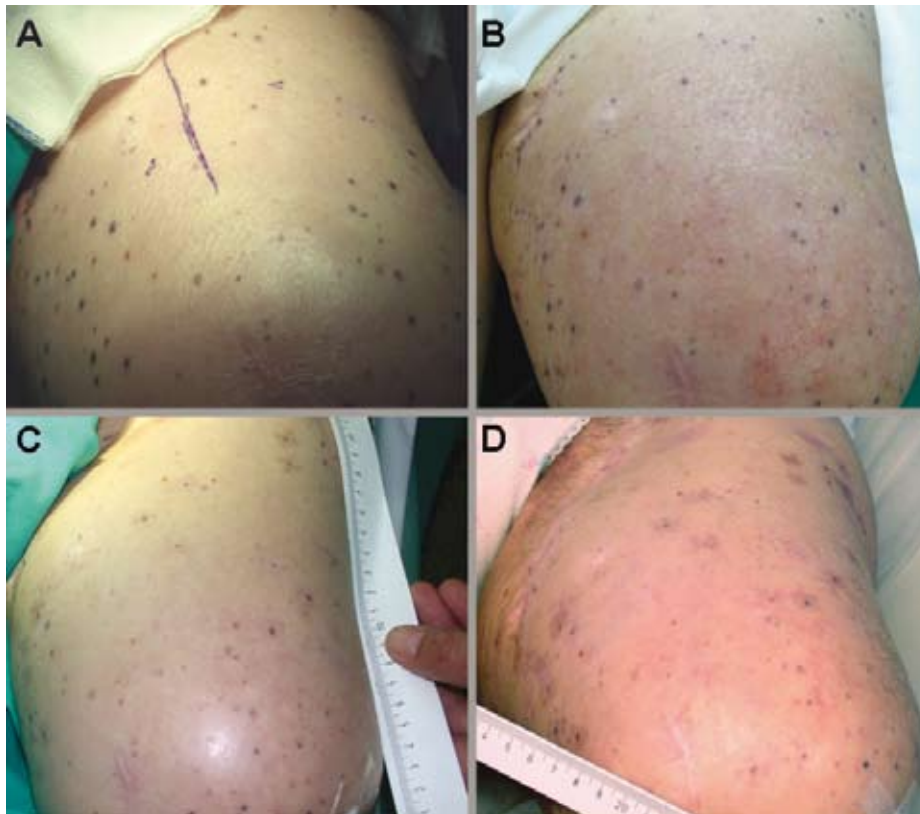


Figure 1. Response of melanoma skin metastases to electrochemotherapy. (A) Multiple unresectable melanoma skin metastases before therapy. Nodules were treated with electrochemotherapy using two different repetition frequencies (right 1 Hz; left 5 kHz). (B) Treatment effectiveness five weeks after the first electrochemotherapy session. The treated tumor nodules had regressed completely, but the skin remained pigmented in some places and that there was no difference in response with regard to the frequency of electric pulses used. (C) Appearance of skin melanoma metastases at the time of the last electrochemotherapy session. Previously treated metastases regressed completely. (D) Long-term follow-up of the treatment effectiveness of electrochemotherapy 9 months after the first electrochemotherapy session.

Discussion

The presented case demonstrated that electrochemotherapy was feasible and effective on multiple melanoma nodules that can be treated in several consecutive sessions. In the first electrochemotherapy session, we compared relative effectiveness of electrochemotherapy using 1 Hz and 5 kHz repetition frequency of electric pulses. In the ESOPE study, the same comparison between the antitumor effectiveness of electrochemotherapy using 1 Hz and 5 kHz was made on nodules from different patients (4). The case with multiple unresectable metastases on the thigh made it possible to further test these two treatment approaches and univocally demonstrate in a single patient that electrochemotherapy is effective regardless of the repetition frequency of the applied electric pulses. Since no difference in response between the two treatment approaches was observed in two months' time after the session, the following three electrochemotherapy sessions were performed using only 5 kHz repetition frequency of the applied electric pulses. This is, therefore, the first clinical case to demonstrate that high repetition frequency is as effective as 1 Hz repetition frequency of applied electric pulses. Although this question has already been dealt with in preclinical studies, the results were not conclusive, since they predominantly demonstrated that high repetition frequency enabled faster application of electric pulses and also induced only one muscle contraction, which is of clinical benefit (16,17).

The case also demonstrated that as many as several hundred cutaneous metastases could be treated successfully by electrochemotherapy. In the study by Rols et al (9), up to 22 melanoma nodules in the thigh were successfully treated by electrochemotherapy with intravenously injected bleomycin. Other studies also reported a successful treatment of numerous small melanoma nodules by electrochemotherapy with intralesional injection of bleomycin, with a high

percentage of complete responses (7,8). These studies, including ours, provide evidence that this approach is feasible and also useful in cases where isolated limb perfusion would be indicated. As many cancer centers have not acquired the necessary technology for isolated limb perfusion, electrochemotherapy can be useful there because this technology is effective, easy to perform, and commercially available. Further clinical studies are needed to confirm this conclusion.

In conclusion, electrochemotherapy with intravenous bleomycin can be a treatment of choice in cases of multiple unresectable cutaneous melanoma metastases for local control of the disease.

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