Successful sphincter-saving treatment of anorectal malignant melanoma with electrochemotherapy, local excision and adjuvant brachytherapy

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Anorectal malignant melanoma is a rare tumor and there is no consensus on whether aggressive or local management is more appropriate. Local sphincter-saving excision has been shown to have a higher recurrence rate than abdominoperineal resection, although there is no long-term survival difference between the two approaches. Therefore, new adjuvant treatment strategies to permit local sphincter-saving excisions are warranted. In our case, a large anorectal malignant melanoma was successfully treated preoperatively by electrochemotherapy with cisplatin that, by reducing the tumor size, enabled sphincter-saving local excision. Brachytherapy was postoperatively delivered to the excision site. Fourteen months after the beginning of treatment, the patient is without signs of local recurrence and is continent. ***Anti-Cancer Drugs*** **16:345–348 © 2005 Lippincott Williams & Wilkins.**

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Introduction

Anorectal malignant melanoma is a rare clinical condition with a dismal prognosis. There are basically two different treatment strategies: aggressive with abdominoperineal resection (APR) and a sphincter-saving procedure with local excision, potentially with adjuvant radiotherapy [1]. Sphincter-saving operations have lately been gaining more proponents as the survival rates are similar to those achieved with the more radical APR [1–3]. Recently, a new method, i.e. electrochemotherapy, has proved effective in local control of malignant melanoma. Electrochemotherapy is a treatment that uses electroporation for enhancing the drug delivery into the tumor cells and thereby increasing drug cytotoxicity [4–7].

We present a case of a patient with large anorectal melanoma that was treated locally with electrochemotherapy in order to reduce the tumor size before local tumor excision was attempted. Fourteen months after the beginning treatment, the patient is without signs of local recurrence and is continent.

Case report

A 52-year-old male patient was referred to our hospital for further management of residual anorectal malignant melanoma that was partly excised as a thrombosed hemorrhoid.

The patient presented with the lesion at the anorectal junction, 3×2 cm in diameter, tumor volume 6.2 cm^3 (Fig. 1A). The sphincter-saving local excision of the lesion was not possible. Colonoscopy did not reveal any further lesions in the rectum or colon. Computed tomography (CT) of the pelvis showed enlarged lymph nodes in the right inguinal region in which fine needle aspiration biopsy showed melanoma metastases. Chest X-rays and abdominal ultrasound (US) did not find any metastatic deposits.

A deep inguinal lymph node dissection and electrochemotherapy of the lesion at the anorectal junction were performed under the same general anesthetic. The patient signed an informed consent form before the procedure and was treated in line with the protocol of the ESOPE study, approved by the EU Commission. The patient was informed about the treatment options. Electrochemotherapy with cisplatin was performed as described previously [6,7]. Briefly, cisplatin (Cisplatyl; Paris, France) was dissolved in water to obtain a concentration of 2 mg/ml and a total dose of 6 mg was injected into the lesion. Electroporation of the lesion was performed at 2–5 min after drug injection. The tumor lesion was exposed to five applications of electric pulses in order to cover the whole tumor area, using needle electrodes. Seven electrodes of 0.7 mm diameter were arranged in a hexagonal array with six outer electrodes

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Fig. 1

Anorectal nodule of malignant melanoma. (A) Before the treatment (3 × 2 cm). (B) Electrochemotherapy treatment, insertion of needle electrodes. (C) Immediately after the first electrochemotherapy session. (D) Day 27, before retreatment with electrochemotherapy. (E) Tumor nodule 4 weeks after second electrochemotherapy session, at the time of radical sphincter-saving local excision (2.5 × 1.7 cm). (F) Region of the treated nodule 1 year after the beginning of treatment.

positioned 8 mm apart and 8 mm from the central electrode. At each application eight electric pulses of 730 V and of 100 µs duration were delivered at a frequency of 5 kHz between each pair of neighboring electrodes (8 mm apart) (Fig. 1B and C). Thus, altogether 192 pulses were delivered at each application. The electrodes and electric pulse generator Cliniporator were provided by IGEA (Carpi, Italy).

After 4 weeks, the tumor nodule that was treated with electrochemotherapy regressed to 2.5 × 1.7 cm (volume 3.8 cm^3) (Fig. 1D) and electrochemotherapy was repeated on this remaining tumor mass (4 mg cisplatin intratumorally, three applications of electric pulses) under general anesthesia. After the second electrochemotherapy session, the lesion became necrotic in the center and ulcerated.

Three weeks later, a macroscopically radical sphincter-saving local excision was performed under spinal anesthesia (Fig. 1E). Histology revealed multiple foci of the recurrent melanoma from 5 to 15 mm, ulceration of perianal skin and invasion of the ischiorectal fatty tissue at the margin of resection. Therefore intracavitary radiotherapy with ^{137}Cs was performed 2.5 months later. A tumor dose (TD) of 10 Gy was delivered to the resection site using a special custom-made applicator. A second application was planned, but not performed because, 2 months later, an in-transit metastasis appeared on the right perineal side. The metastasis was excised and externally irradiated with TD of 50 Gy. Four months after the completion of radiotherapy, examination revealed an enlarged left inguinal node. A deep inguinal dissection was performed, revealing metastases in three out of 18 lymph nodes. The inguinal region was postoperatively irradiated with TD of 46 Gy. Further staging studies were performed at this time. No evidence of metastasis was observed on chest X-ray, US of the liver or CT of the liver. Several in-transit metastases were discovered on US examination of the right inguinal region. Four cycles of chemotherapy with dacarbazine (800 mg/m^2, single dose) were given, following which regression was observed in the inguinal metastases.

Fourteen months after the beginning of treatment, the patient is without signs of local recurrence and has no problems with defecation or continence (Fig. 1F).

Discussion

Anorectal malignant melanoma is an uncommon condition accounting for about 1% of all melanomas [8]. Approximately 500 cases have been documented in the literature [3]. The disease is characterized by an early systemic spread and generally poor prognosis. Typically, it develops in the sixth or seventh decade of life. The traditional therapy of patients with distant metastatic sites consisted of complete surgical excision, followed by systemic agents. Surgical procedures ranged from APR to local excision alone. Although APR was reported to have resulted in improved loco-regional control rates (70% local control after APR versus 35% after local excision), there was no difference in long-term patient survival after treatment by either operation [1,2]. Therefore, it was difficult to advocate the functionally debilitating APR if local excision, combined with an adjuvant local treatment in order to reduce the local recurrence rate, could be as effective as APR. In patients treated by local excision and adjuvant radiotherapy treatment, results were good [1]. However, as the results of local excision seem to be inadequate in terms of long-term local control, new treatment strategies are warranted. We presented a case of anorectal malignant melanoma treated locally by electrochemotherapy with cisplatin in order to reduce the tumor since local excision might not have been possible due to the size and location of the tumor.

Electrochemotherapy consists of chemotherapy followed by local application of electric pulses to the tumor to increase drug delivery into the cells [4,9]. Thus, the enhanced drug delivery can substantially potentiate chemotherapeutic drug cytotoxicity locally at the site of electric pulse application, without affecting drug effectiveness in the tissue that was not exposed to electric pulses. Preclinical studies demonstrated that the electroporation of cells could increase several fold the cytotoxicity of bleomycin and cisplatin [4,9]. Antitumor effectiveness of electrochemotherapy was demonstrated also *in vivo* on different animal tumor models [4,10]. The increased antitumor effectiveness was shown to be due to the increased drug accumulation in the tumors and cells, drug entrapment in the tumors, and the antivascular effect of electrochemotherapy due to the cytotoxic effect of electrochemotherapy on endothelial cells [9]. Based on the data from preclinical studies, several clinical studies on electrochemotherapy using bleomycin and cisplatin administered either locally or systemically were initiated. Cutaneous metastases of different tumors were treated, such as head and neck squamous cell carcinoma, malignant melanoma, basal cell carcinoma, adenocarcinoma of the breast and salivary gland, hypernephroma, Kaposi sarcoma, and transitional cell carcinoma of the bladder. Altogether, 727 nodules in 138 cancer patients were treated. Overall results in those studies showed that electrochemotherapy is an effective treatment; objective responses were obtained in 48–100% of the treated nodules [6,7]. Antitumor effectiveness of electrochemotherapy with cisplatin on malignant melanoma was demonstrated in two studies [5,6]. The first of these studies unequivocally demonstrated a superior response rate in tumors treated by electrochemotherapy with cisplatin (77%) compared to those treated with cisplatin alone (19%) [5]. The second study confirmed the results of the first study, demonstrating that 293 nodules in 24 patients treated by electrochemotherapy with cisplatin resulted in 81% objective responses; of these, 69% of nodules showed a complete response [6].

Anorectal malignant melanoma is a disease with poor prognosis [11]. The median survival of patients is 25 months [3]. Although there is a case of a patient treated with local excision only who survived for 10 years [3] and another case of a patient with positive inguinal lymph nodes who survived for 21 years [2], local excision tends to have more local recurrences than APR and nodal disease has a grave prognosis [2]. Our patient had nodal disease and a large primary melanoma at the time of presentation. In light of these facts, we decided to treat the patient by local excision in order to improve his quality of life. As the primary tumor was large (3 cm in diameter), we tried to reduce its size with electrochemotherapy before the local excision. After two electrochemotherapy sessions, resulting in reduced tumor size and necrosis with central ulceration, a macroscopically

clean surgical margin was obtained by local excision. Later on, histology revealed microscopic positive margin on the side of ischiorectal fossa; we applied brachytherapy to the site of local excision. Fourteen months after the beginning of treatment, the patient is without signs of local recurrence and has no problem defecating.

In conclusion, we can say that local treatment with electrochemotherapy with cisplatin proved to be a good treatment strategy for reducing the tumor size before sphincter-saving local excision.

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