Electrochemotherapy with cisplatin in successful sphincter-saving treatment of anorectal malignant melanoma

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 sphincter-saving procedure with local excision, potentially with adjuvant radiotherapy. Sphincter saving operations has lately been gaining more proponents as the survival rates are similar to those achieved with the more radical APR. In the case report 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 Institute of Oncology Ljubljana 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 x 2 cm in diameter, tumor volume 6.2 cm³ (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. Electrochemotherapy with cisplatin was performed as described previously. Briefly, cisplatin at a total dose of 6 mg was injected into the lesion, 2-5 minutes thereafter electroporation of the
lesion was performed. The tumor lesion was exposed to 5 applications of electric pulses in order to cover the whole tumor area, using hexagonal needle electrodes (Fig. 1B,C). The electrodes and electric pulses generator CLINIPORATOR™ were provided by IGEAS.r.l., Carpi, Italy.

After 4 weeks, the tumor nodule that was treated with electrochemotherapy regressed to 2.5 x 1.7 cm (volume 3.8 cm³) (Fig. 1D) and electrochemotherapy was repeated on this remaining tumor mass (4 mg cisplatin intratumorally, 3 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 mm to 15 mm, ulceration of perianal skin, and invasion of the ischiorectal fatty tissue at the margin of resection. Therefore intracavitary radiotherapy with Cs137 was performed 2.5 months later. Tumor dose (TD) of 10 Gy was delivered to the resection site.

Two months later, an intransit metastasis appeared on the right perineal side that 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 3 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 ultrasound examination of the right inguinal region. Four cycles of chemotherapy with dacarbazine (800 mg/m², 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 a disease with poor prognosis. The median survival of patients is 25 months. Although there is a case of a patient treated with local excision only who survived for 10 years and another case of a patient with positive inguinal lymph nodes who survived for 21 years, local excision tends to have more local recurrences than APR and nodal disease has a grave prognosis. Our patient had nodal disease and a large primary melanoma at the time of presentation. In the 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.

M. Snoj, Z. Rudolf, G. Serša

The case report is presented based on the original article:


Naked DNA:
DNA molecules, usually plasmids, that are not linked to or complexed with proteins, lipids or other artificial molecules. Naked DNA is stable, but is not protected towards the degradation by specific enzymes. It cannot cross the membrane of the cells, and in vitro it is unable to penetrate the cells and to express its genetic information inside the cells. However, in vivo, naked DNA can be taken up by some cells by a slow and inefficient mechanism resulting in the low and extremely variable expression of its genetic information in these cells of the organism.

Gene therapy:
Gene therapy is an emerging medical technique that involves the addition of genes into individual cells and tissues to treat a disease, and in particular hereditary diseases. An hereditary disease is characterized by the presence in the genes of abnormal sequences: when a gene is damaged, the blueprint for the construction of the protein it codes for is imperfect and the resulting protein is therefore abnormal. The goal of gene therapy is to cure a genetic disease by introducing a normal copy of the gene into the cells containing the damaged version, in order to re-establish the presence and the function of the corresponding normal protein. Although the technique is still in its infancy, it has been used successfully to treat genetic disorders such as the severe combined immune deficiency in children. Usually, experimentally modified virus are used to transport the sequences of interest into the deficient cells since virus have been naturally selected, for millions of years, to transfer their own genes into all types of cells, including plant, animal and human cells.

Non viral gene therapy:
The term 'non-viral' describes, rather loosely, all the gene transfer strategies that do not use any kind of virus or of viral sequences to introduce the genes of interest into the target cells. These techniques range from the simple injection of naked DNA to the use of sophisticated gene guns were DNA is deposited in very small gold particles that are projected towards the cells. Non-viral gene delivery systems have been devised using physical or chemical approaches. Chemical approaches consist in the encapsulation of the DNA in liposomes or microspheres, in the adsorption of DNA onto nanoparticles, or on the complexation of DNA with cationic lipids. These techniques are performing well in vitro but they are useless in vivo. Physical techniques include the gene guns and the jet injections for surface exposed sites, the delivery of electrical pulses or even of ultrasounds. The use of electric pulses (DNA electrotransfer, gene electrotransfer, or electrogeneetherapy) has been proven to be quite efficient and useful for gene transfer to normal and tumor tissues in animal organisms.

PARTNER SC1:
Laboratory of Biocybernetics, Faculty of Electrical Engineering, University of Ljubljana

Laboratory of Biocybernetics was founded in 1963 by the late Academician Professor Lojze Vodovnik, who also headed it until his retirement in 1998. Since then, the head of the laboratory is Professor Damijan Miklavčič. The research in the 1960s and 1970s was mainly focused on functional electrical stimulation (FES) of the extremities, with the primary purpose of restoring impaired motoric functions caused by various neuromuscular diseases. Considerable success was achieved in...
Many of the ideas developed in the laboratory have been adopted by rehabilitation centers throughout the world. Since 1980s, the main focus of research shifted to the investigations of the influence of electromagnetic fields and electric currents on the physiological state of cells, tissues, organs, and the body as a whole. The aims are to understand the basic mechanisms of bioelectric phenomena and to facilitate their use for therapeutic purposes. Major directions are cell membrane electroporation with its applications in electrochemotherapy of tumors (ECT) and electrogene therapy (EGT), electrical stimulation of chronic wound healing and non-invasive measurements of tissue perfusion and oxygenation. The laboratory is also involved in development of electronic devices for application in these fields of research, as well as information technology for clinical trials. In addition, to gain an insight into the studied phenomena, the distribution of electric currents and electromagnetic fields within cell suspensions and tissues are modeled, implementing both analytical and numerical techniques. The research results are regularly presented in articles in SCI-ranked scientific journals (50 articles in 2000-2004), as well as at international scientific conferences and meetings. A detailed description of the research work, as well as a comprehensive bibliography can be found on the lab's home pages (http://lbk.fe.uni-lj.si).

Laboratory of Biocybernetics was involved in the CLINIPORATOR and ESOPE projects of the 5th European Framework, and is one of the partners on the forthcoming ANGIOSKIN project of the 6th European framework, where the purpose will be the electrotransfer of therapeutic genes into the skin for treatment of acquired or inherited skin diseases.

At the time of writing, the laboratory has 18 regular members and several associated members. The students at the Faculty of Electrical Engineering are encouraged to join the research work, and several students do so each year, some also in the very first year of undergraduate studies at our faculty. After graduation, some students pursue a postgraduate course, deepening and broadening their knowledge, and two to three postgraduate students obtain their M.S. or Ph.D. degrees in the laboratory each year.

T. Kotnik

More information and contacts on Laboratory of Biocybernetics are available on: http://lbk.fe.uni-lj.si