Oral etoposide in Merkel cell carcinoma

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SUMMARY

Background Merkel cell carcinoma (MCC) is a very infrequent and aggressive skin tumor with high recurrence and metastasis rates. MCC treatment is currently not well defined.

Case presentation We present the case of a 75-year-old woman who was diagnosed with MCC in 2010 and suffered a third relapse in 2012 which could not be treated surgically.

Results The patient began oral etoposide treatment reaching complete response after eight cycles and receiving a total of 11 cycles. As side effects, the patient suffered from neutropenia, candidiasis and mucositis, but after reducing the dosage to 50% it was well tolerated.

Discussion Chemotherapy treatment in this setting is poorly defined. In this case, monotherapy treatment with oral etoposide was decided due to the patient's age and comorbidities, achieving a very positive outcome.

BACKGROUND

Merkel cell carcinoma (MCC) is a very infrequent and aggressive skin tumour which is classified as a neuroendocrine carcinoma.^{1–3}

Although the definitive cell of origin for MCC has not yet been determined, this tumour is generally considered to arise from Merkel cells, which are found in the skin and some areas of the mucous membrane. Most of them are associated with nerve fibres, acting as type I mechanoreceptors⁴; others are found in the skin unrelated to nerve endings, as part of the diffuse neuroendocrine system.³

MCC is more frequent among the Caucasian population aged over 60. In younger patients, the tumour usually occurs in those who are immunosuppressed, such as HIV positive and transplant patients.³ MCC has also been related to polyomavirus infection.⁵ The most frequent location for this tumour is in sun-exposed skin areas, especially head and neck (50%) and extremities (40%). MCC is clinically characterised by the presence of fast and infiltrative growth asymptomatic lesions, normally appearing as papules, plaques or nodules.³ MCC shows high rates of recurrence, lymphatic nodule involvement and metastasis.³ It is estimated that local recurrence occurs in 25–30% of cases, with metastasis in 34–36% of patients. The 5-year survival rate ranges from 30% to 64%.⁶

In general terms, due to local aggressiveness and the tendency to relapse, initial therapy consists of wide exeresis, as well as regional lymphadenectomy in those patients with affected lymph nodes.^{1 2 6} In some cases, adjuvant radiotherapy is recommended in the lesion area. According to the literature,^{2 3 7} the use of radiotherapy and surgery gives better results than surgery alone, showing higher benefits

in those cases when an adequate resection is not achieved or when there are affected margins.^{3 7}

Chemotherapy is not normally the first option for this type of tumours due to patients' age and comorbidities, with a dubious risk-benefit ratio. For this reason and because of the low prevalence of the disease, very few data are available on the effectiveness of chemotherapy in these patients.

CASE PRESENTATION

We present the case of a 75-year-old woman. Her previous history included an intracranial haemorrhage episode, low-grade endometrial cancer treated by hysterectomy, hypothyroidism, hyperuricaemia and hypercholesterolaemia. In 2010 she was diagnosed with MCC in the frontal region. Lesion resection with a 1.5 cm margin and reconstruction using a Limberg flap was performed. In 2011 she presented with relapse in the frontal region, which was also surgically treated. In 2012 the patient presented with a new right temporal and cervical relapse. After deciding against surgery and radiotherapy, it was decided to begin chemotherapy treatment.

INVESTIGATIONS

In order to decide the best chemotherapy treatment for the patient, the oncologist and the hospital pharmacist did a bibliographic research with the following findings.

There are two different views on the approach to MCC treatment. One point of view advocates that MCC management is similar to other non-melanoma skin tumours and considers surgery and radiation to be the only therapies. The other point of view favours treatment with systemic chemotherapy because of the analogy between the biological properties of MCC and lung cancer.^{8 9}

Existing data confer a limited role on chemotherapy, setting it aside in many cases as a palliative treatment due to its lack of clear benefit for survival and relapse prevention,^{2 6 7 10–12} even presenting negative effects regarding associated morbidity and mortality due to its adverse side effects.² However, the high relapse rate of this tumour makes some authors defend its usage, recommending it especially for high-risk cases.¹³

In general terms, systemic treatment is reserved for locally advanced metastatic cases or for those which cannot be approached surgically, considering each patient on an individual basis.

Available data on the use of chemotherapy for MCC come from retrospective studies and case series using various agents. The National Comprehensive Cancer Network (NCCN) recommends one of the following regimes:⁶ the combination of

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etoposide and cisplatin or carboplatin, the combination of cyclophosphamide with doxorubicin and vincristine, monotherapy with topotecan. In the TROG study,¹³ a favourable response was observed in patients with MCC treated with intravenous chemotherapy following an etoposide and cisplatin regime.

TREATMENT

In this case, treatment with etoposide was chosen based on the analogy of MCC with small-cell lung carcinoma. Etoposide is a semisynthetic podophyllotoxin derivative which interferes with topoisomerase II function. It is indicated for the treatment of certain antineoplastic diseases such as testicular tumours, small-cell lung carcinoma and some haematological tumours. The use of etoposide for MCC treatment has been mainly in intravenous administration as part of a combined regime with other agents, especially cisplatin or carboplatin.⁶ We decided to use monotherapy with oral etoposide because of the patient's age and comorbidities. The procedure for off-label use was undertaken.

The patient began treatment in August 2012 at a daily dosage of 100 mg for 10 consecutive days every 28 days.

OUTCOME AND FOLLOW-UP

Five days after ending the first chemotherapy cycle the patient presented with mucositis and candidiasis and was found to have a neutrophil blood cell count of 880. Because of these adverse effects, the dose of etoposide was reduced to 50% beginning with the second treatment cycle.

In the control before the fourth cycle, a clinical response of >50% was obtained. In the month of March, after eight cycles, a complete response was achieved and it was decided to maintain the treatment until completion of 11 cycles.

The patient continued under periodic follow-up. Three years later, in December 2015, the patient died due to non-oncological causes, having maintained a complete response until then.

DISCUSSION

MCC treatment is currently not well defined. In this case the initial approach was surgical as this is the treatment with the highest effectiveness and lowest relapse rate.^{1 2 6} Following a third relapse and after discarding surgery and radiotherapy, the only available approach was chemotherapy. The chemotherapy treatment plan for MCC is not well defined; the analogy shown with small-cell lung carcinoma was decisive when choosing a treatment. This scheme resulted in neutropenia with candidiasis and mucositis but, after reducing the dosage to 50%, it was well tolerated. Even after the dosage reduction the treatment was highly effective.

Our patient exhibits similarities with other cases described in the literature. In a study by Schlaak *et al*,¹⁴ four patients with a median age of 68.5 years were treated with oral etoposide, three of whom achieved complete remission. Also, in a study by Fenig *et al*,¹⁵ three patients received oral etoposide (in these cases all patients had been treated with intravenous etoposide previously) and two of them showed a complete response. In these cases, as in the one we describe, the drug was well tolerated with the main side effect reported being haematological toxicity.

Chemotherapy for MCC is poorly defined due to the low prevalence of the disease and because it is mainly treated surgically.

To define the role of chemotherapy in these patients more clearly, it would be highly desirable for clinical trials to endorse its efficiency and safety but, because of their scarcity, it is especially important to communicate cases such as the one presented here. In this case, a non-innovative and low-cost drug was used for the treatment which resulted in a very positive outcome.

Learning points

- ▶ When deciding the best treatment for a patient, we have to consider all the patient's characteristics including age and comorbidities.
- ▶ Off-label use of drugs can be very effective but it is necessary to do an extensive bibliographic search to gather all the information about the use of the drug in that setting.
- ▶ Non-innovative low-cost drugs can be as effective as new drugs to treat oncological patients.
- ▶ When we are facing a difficult clinical case, it is essential to work as a multidisciplinary team to achieve the best possible outcome.

Competing interests None declared.

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