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GENERAL INFORMATION

Cutaneous melanoma and the new drugs☆

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Abstract The treatment of cutaneous melanoma has historically been essentially surgical. Much progress has been made in this area, and the resection margins have been established based on tumour depth. Candidates are also identified for lymphadenectomy, avoiding the morbidity of the procedure in patients who do not require it. But little progress has been made in systemic treatment, since the 70's when the use of dacarbazine was introduced for the treatment of patients with tumour progression or distant metastasis, with disappointing results. Despite this, dacarbazine has been the most used drug to the present.
Three years ago, two new drugs were introduced, one of them based on the target therapy and other one in the immunotherapy, offering, with the obtained results, an alternative in the treatment of cutaneous melanoma.
The objectives of this article are to show the pathways of these drugs, to describe the current role of surgery in cutaneous melanoma, with the arrival of these drugs, as well as to know the therapeutic alternatives that are emerging for the cutaneous melanoma based on scientific evidence.

PALABRAS CLAVE
Melanoma;
Tratamiento de melanoma

La cirugía en melanoma cutáneo maligno y las nuevas drogas

Resumen El tratamiento del melanoma cutáneo ha sido, históricamente, esencialmente quirúrgico. Muchos progresos se han hecho en esta área: se han establecido los márgenes de resección con base en la profundidad del tumor y, se han identificado pacientes candidatos a linfadenectomía, evitando así la morbilidad del procedimiento en pacientes que no la requieren.

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Pero en el tratamiento sistémico se han hecho escasos progresos: desde los años setenta se introdujo el uso de la dacarbazina para el tratamiento de los pacientes con progresión tumoral o metástasis sistémicas, pero los resultados han sido decepcionantes; a pesar de ello, la dacarbazina ha sido la droga más utilizada hasta la actualidad.
Hace 3 años, 2 nuevas drogas fueron introducidas, una de ellas basada en la terapia blanco y la otra en la inmunoterapia, ofreciendo una alternativa en el tratamiento del melanoma cutáneo. Los objetivos de este manuscrito son: mostrar las vías de acción de estos medicamentos. Describir cuál es el papel actual que tiene la cirugía en el tratamiento del melanoma cutáneo con la llegada de estas drogas, y conocer qué alternativas terapéuticas están surgiendo para el tratamiento sistémico del melanoma cutáneo con base en la evidencia científica.

Background

Since 1971, dacarbazine has been the standard treatment for patients with systemic inoperable metastases of malignant melanoma.[1] It produces global responses in approximately 15% of patients, but in only 4% the disease disappears, and in those with full response the interval free of disease is very short; the mean recurrence is 3–6 months.

Recently, a great variety of effective drugs for the treatment of bronchogenic cancer, breast cancer, colorectal cancer and other tumours have appeared, turning the treatment of these neoplasms into a multidisciplinary exercise; while for cutaneous melanoma the treatment is still within the field of only one discipline: surgery.

The progress in the treatment of other neoplasms has far overtaken that of melanoma. Cutaneous melanoma has proven to be, more than other neoplasms, insensitive to the various systemic therapies and radiotherapy. This may be due to the fact that the cells from which melanoma originates are designed to protect it against the damages of DNA caused by the sun, and are located in the skin, where they are exposed to the damage caused by UV rays on the DNA. These cells seem to have the ability to defend themselves when exposed to cytotoxic drugs, similarly to how they do in the hostile environment where they normally develop.

This does not mean that there have been no developments in the therapy of cutaneous melanoma; substantial developments have been made in the understanding of the behaviour of this neoplasm and its surgical treatment. Resection margins were substantially reduced based on solid scientific evidence; it was proved that prophylactic lymph node dissection and regional perfusion were not useful and these were abandoned; lymphatic mapping with biopsy of sentinel lymph node was introduced, and it was proved that it improved staging, which offered valuable information for the prognosis, which in selected patients avoided unnecessary morbidity caused by lymph node dissection, and that it improved the survival of patients with a positive sentinel lymph node.[2]

In the staging and diagnosis, it was proved that positron emission tomography improved the staging of patients with advanced disease. As a result of these developments, the treatment of malignant melanoma became more individualised and survival rates improved; however, melanoma experts are still waiting for a really effective drug for the systemic treatment of patients with systemic disease.

Changes arrived in 2010, when there were 2 relevant developments in systemic therapy: targeted therapy and immunotherapy.

Targeted therapy

Targeted therapy is related to the tyrosine-kinase pathway, also known as MAP Kinase pathway or MAPK signalling pathway (Fig. 1). This pathway begins in the cellular membrane

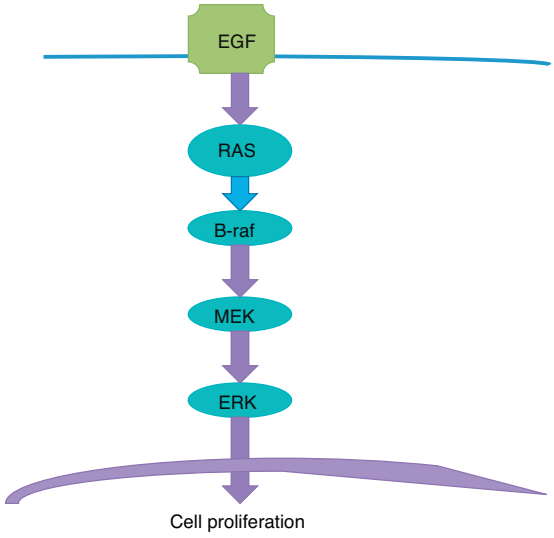

Figure 1 The tyrosine-kinase pathway begins in the receptor of the epidermal growth factor (EGF) of the cellular membrane and goes through a series of steps towards the nucleus.