

Treatment of Merkel cell carcinoma with radiotherapy and imiquimod (Aldara): a case report

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ABSTRACT

Aims and background. Merkel cell carcinoma (MCC) is a rare skin tumor occurring mostly in older people. Postoperative radiotherapy is strongly recommended to improve local control. A case of a MCC treated by radiotherapy associated with imiquimod (Aldara) is presented. A possible physiopathological rationale for this concomitant treatment is also given.

Materials and methods. We treated a diabetic 82-year-old man presenting with a MCC of the right zygomatic area. Despite surgery, postoperative ultrasonography showed a firm, painless residual mass of about 11 × 10 cm, fixed to the deep tissues. Parotid and zygomatic areas were treated along with the ipsilateral laterocervical lymph nodes. The total dose to the planning target volume was 50.4 Gy (1.8 Gy/day). Imiquimod was applied once a day to the zygomatic area with macroscopic infiltration and to the surrounding erythema.

Results. During the combination treatment, the patient showed acute G3 skin toxicity (RTOG) and a scab that resolved after a 3-week interruption of the radiotherapy and imiquimod treatment. When the scab was removed, the underlying skin appeared completely re-epithelialized. Imiquimod was suspended and treatment was continued only with irradiation. During this second phase of the treatment, the patient developed G2 dermatitis and G2 stomatitis. Clinical and instrumental re-evaluation showed a complete response 7 months after the end of radiotherapy, with very good local tropism.

Conclusion. This case report suggests the possible effective use of immunomodulators, in this case imiquimod, combined with radiation therapy for cutaneous malignancies such as MCC. Skin tolerance should be an important issue to consider. Free full text available at www.tumorionline.it

Introduction

Merkel cell carcinoma (MCC) is a rare, highly malignant primary skin tumor of neuroendocrine origin, originally referred to as trabecular carcinoma¹. More than 400 new cases of MCC occur in the United States each year, and the mortality rate is approximately 25%. MCC differs from other skin cancers because it is more aggressive and develops rapidly over a few weeks or months.

Tumor stage at the time of diagnosis greatly influences the prognosis of MCC patients. Small tumors (less than 2 cm) without nodal spread have a 5-year survival rate exceeding 90%. Patients with nodal involvement have a 5-year survival of about 50%. The disease recurs in about 50% of patients and the reported mortality rates are 20-55%².

Because of its rarity and poor prognosis, MCC poses a challenge to the clinician. Standard treatment of clinically localized disease is wide excision with a tumor-free

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margin of at least 2 cm, when possible. Because of its radiosensitivity, adjuvant radiotherapy has been advocated in MCC in order to improve local control in locoregional disease. Several clinical studies have suggested that the risk of local recurrence and regional (nodal) metastasis may be significantly lower in patients who undergo adjuvant radiotherapy following surgery³⁻⁵.

However, surgery is sometimes difficult because MCC often occurs in older people with health problems that may be incompatible with general anesthesia. In these cases, radiotherapy is the only therapeutic option with demonstrated efficacy and good local control^{6,7}. The administered dose of RT ranges from 30 to 70 Gy, with most reported patients receiving 45-50 Gy⁸.

In inoperable patients, radiation therapy can be applied to the primary tumor, with elective treatment of clinically uninvolved nodes. There is evidence that salvage surgery and radiation for recurrent locoregional disease and the addition of chemotherapy in the presence of distant metastasis can improve survival⁹, but this aggressive, potentially toxic approach may have limited applicability in this elderly population.

Material and methods

An 82-year-old man suffering from diabetes and treated with dialysis for chronic renal insufficiency presented an MCC of the right zygomatic area. He underwent surgery, but ultrasonography performed 2 months later showed residual disease. Because of the age and clinical condition of the patient, the surgeon decided not to perform another surgical procedure. When the patient came to our observation several months later, the lesion was about 11 × 10 cm, firm, prominent on the skin for about 1.5 cm, and fixed to the deep tissues (Figure 1). He had been using imiquimod cream on the lesion once a day, 5 applications/week, without any efficacy.

The area was measured and photographed, and diagnostic biopsy specimens were obtained from the lesion before the initiation of radiation therapy. Parotid and zygomatic areas and the ipsilateral laterocervical lymph nodes were treated with 2 angled fields. The total dose to the planning target volume (PTV) was 5040 cGy (180 cGy/day) delivered with a 6-MV LINAC. Throughout the radiotherapy period the patient received applications of imiquimod once a day on the zygomatic area affected by macroscopic infiltration and the surrounding erythema.

After 12 treatment sessions (2160 cGy), acute skin toxicity (G3 according to the RTOG criteria) developed, with a large scab on the treated area. This acute reaction cleared up with a 3-week interruption of the combined treatment. When the scab was removed, the underlying skin appeared completely re-epithelialized. For this reason we decided to suspend concurrent imiquimod, continuing treatment only with radiation therapy. During



Figure 1 - Disease situation at the time of diagnosis.

this second treatment phase the patient experienced G2 dermatitis and G2 stomatitis, but he completed the radiotherapy without other interruptions. At the end of radiotherapy, clinical evaluation showed a complete response.

CT scan of the thorax and clinical evaluation of the treated area performed 7 months after the end of radiotherapy did not show any sign of local recurrence and/or metastatic disease, with very good local tropism (Figure 2).

Physical examination showed a lesion of the trunk that was highly suspicious for MCC. After surgical removal, MCC was histologically confirmed. The patient died of other causes 9 months after the end of therapy, showing no local recurrence.

Discussion

It is generally recognized that case reports are not representative of the average case, but it is also evident that clinical observations are not totally useless. Clinical decisions are generally driven by a combination of evidence and judgment. As Greenhalgh puts it, "The clinical method is an interpretive act which draws on narrative skills to integrate the overlapping stories told by patients, clinicians and test results"¹⁰. An editorial in Dermatology appears to confirm this concept¹¹.

We present our own experience against this background of evidence-based case reports. Although it remains to be elucidated how radiation can influence tu-



Figure 2 - Complete response 7 months after the end of combination treatment.

mor immunogenicity, data from preclinical studies have provided proof of principle that different immunotherapeutic strategies can be combined with radiotherapy to enhance the antitumor effect¹²⁻¹⁴. Here we describe the first reported use of imiquimod concomitantly with radiotherapy. The decision to try such a particular approach was taken considering both clinical and biological aspects.

Even if radiation therapy can be employed for medically intractable or surgically inoperable MCC, larger lesions may be difficult to eradicate by radiotherapy alone. Concomitant radiochemotherapy has been proposed for these patients¹⁵, although the efficacy of adjuvant chemotherapy remains unproven. Studies have shown response rates of around 60% in locally advanced or metastatic disease with chemotherapy regimens similar to those used for patients with small cell lung cancer⁸. In patients with unresected tumors or resected tumors with microscopic evidence of spread beyond the resection margins, higher doses of 56-65 Gy have been recommended in accordance with the NCI guidelines¹⁶. A higher total dose, however, may increase the risk of acute radiation toxicity, particularly dermatitis and mucositis. The age and comorbidities of the patient of this report (particularly the chronic renal disease) made this approach impossible.

The need to avoid the use of chemotherapy and to reduce the total radiotherapy dose were the reason why

we attempted imiquimod concurrently with radiation therapy. There is biological and clinical evidence to support our approach.

Biologically, it is becoming clear that cancer progression is not sustained by the tumor cells alone but also by the host microenvironment¹⁷. Host fibroblasts are associated with tumor cells at all stages of cancer progression, and their structural and functional contributions to this process are beginning to emerge.

Growth factors, chemokines and extracellular matrix proteins produced by fibroblasts facilitate the recruitment of endothelial cells and pericytes¹⁸. As cancer progresses, tumor-associated host cells may obtain phenotypes that are different from those normally seen in the tissue. For example, the molecular signature of tumor endothelial cells is distinct from that found in endothelial cells in normal tissue¹⁵, providing evidence for crosstalk between the tumor and the host orchestrated by biological factors in the host microenvironment. Interactions between tumor cells, activated host cells, and the dynamic microenvironment in which they live enable tumor growth and dissemination. Mediators of the inflammatory response such as cytokines, free radicals, prostaglandins, and growth factors can induce genetic and epigenetic changes including point mutations in tumor suppressor genes, DNA methylation, and post-translational modifications. This will cause alterations in critical pathways responsible for maintaining the normal cellular homeostasis and will lead to the development and progression of cancer¹⁹. It is becoming evident that early and persistent inflammatory responses in or around developing neoplasms regulate many aspects of tumor development (matrix remodeling, angiogenesis, malignant potential) by providing diverse mediators implicated in maintaining tissue homeostasis.

The complex mode of action of imiquimod is based on its agonistic activity towards Toll-like receptors TLR-7 and TLR-8, and on the subsequent activation of the central transcription factor NF-kappaB. This stimulates the production of proinflammatory cytokines, chemokines and other mediators, resulting in proapoptotic activity against tumor cells. The induction of apoptosis by imiquimod appears to be dependent on Bcl-2 proteins and involves caspase activation. An exhaustive description of the different proapoptotic pathways and their antitumor effects is beyond the scope of this article, but it is important to consider that imiquimod's activity probably depends on its activation of one of these pathways. Recent evidence suggests that radiation therapy may also activate effectors of innate immunity through Toll-like receptor-dependent mechanisms, thereby augmenting the adaptive immune response to cancer²⁰.

Topical application of 5% imiquimod cream has been shown to be effective in the treatment of both nodular and superficial basal cell carcinomas²¹ and may be therapeutically active against cutaneous melanoma metas-

tases and other cutaneous malignancies. Scott reported an apparent response of cutaneous Merkel cell tumor to topical imiquimod, confirming the possible effective role of this molecule in treating MCC²².

Conclusion

Considering its biological and clinical background, we thought that imiquimod could enhance the antitumor efficacy of radiotherapy through a possible synergistic effect of radiation and TLR-targeted immunotherapy. This case report seems to suggest that the use of immunomodulators such as imiquimod in combination with radiation therapy can be effective in selected case where chemotherapy is not possible.

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