Delayed but Complete Response following Oral Temozolomide Treatment in Melanoma Leptomeningeal Carcinomatosis

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Key Words
Temozolomide · Melanoma · Leptomeningeal carcinomatosis · Delayed response

Abstract
Isolated leptomeningeal recurrence of melanoma is rare, occurring in 2% of patients with central nervous system involvement secondary to melanoma. The optimal treatment of leptomeningeal carcinomatosis (LMC) in melanoma has not yet been determined and remains a major challenge. We report a melanoma patient who presented with isolated LMC in the form of a new-onset weakness of the lower limbs, paresthesia of the left hand and foot, lumbago and headache. A lumbar puncture and spinal MRI confirmed LMC. The patient was treated with temozolomide 75 mg/m²/day on a 4 weeks on/2 weeks off schedule. After an initial transient clinical deterioration, the patient showed a complete radiological response as well as a dramatic improvement in quality of life. The encouraging clinical response reported here suggests that dose-intensified temozolomide might have significant activity in the treatment of leptomeningeal dissemination of melanoma and may be a valid treatment option for patients who have not been previously exposed to this agent. Moreover, this treatment regimen is extremely well tolerated and obviates the need for repeated intrathecal administrations of chemotherapeutic agents, which are often not well tolerated by patients who have significant co-morbidities due to their disease. As illustrated in this case, response to temozolomide may occur in a delayed manner, highlighting the importance of following temozolomide treatment long enough before determining that it is inefficient in a given patient.
Introduction

The involvement of the central nervous system (CNS) frequently complicates the clinical course of malignant melanoma. Around 12–16% of all brain metastases have a melanomatous origin, and CNS metastases are estimated to develop in 30% of stage IV melanomas [1]. According to a recent series of 355 cases [2], most patients (90%) have parenchymal metastases whilst only a minority suffers from leptomeningeal metastases [2]. Leptomeningeal carcinomatosis (LMC) is defined as malignant infiltration of the pia mater and arachnoid membrane. LMC from melanoma is not uncommon and represents 5–10% of all LMCs [3]. It usually occurs late in the course of disease and in the presence of extensive systemic dissemination or with associated brain parenchymal metastases. Median survival with LMC is about 4 months, and the patients’ quality of life is severely impaired [2]. Isolated leptomeningeal recurrence of melanoma is rare, occurring in 2% of patients with CNS involvement secondary to melanoma [2]. The optimal treatment of LMC in melanoma has not yet been determined and remains a major challenge [4]. We report a melanoma patient with isolated LMC showing an impressive benefit from systemic treatment with temozolomide.

Case Report

In 1996, our patient underwent local resection of a melanoma (Breslow thickness unknown) on the left lateral thoracic wall. At that time, he was 50 years old. Nine years later, he presented with multiple axillary and supraclavicular adenopathies that were treated by lymph node dissection followed by focal irradiation (40 Gy), as the pathology showed >40 involved lymph nodes. He was subsequently included in a vaccine trial with Melan-A peptide. One year later, mediastinal lymph node metastases were revealed by cough and chest pain, and 6 cycles of cisplatin (20 mg/m² on days 2–5), vinblastine (1.6 mg/m² on days 1–5), dacarbazine (800 mg/m² on day 1) and interferon alpha (5 × 10⁶ IU on days 1–5) were administered over the course of 6 months, leading to a complete clinical and radiological response.

However, 3 months later, the patient presented with a new onset of weakness of the lower limbs, paresthesia of the left hand and foot, lumbago and headache. A brain MRI was unremarkable, while a spine MRI showed multiple contrast-enhancing lesions coating the entire spinal cord as well as the lumbar and sacral nerve roots (fig. 1a, b). A lumbar puncture confirmed LMC of the melanoma (fig. 2a, b). The patient was started on temozolomide 75 mg/m²/day on a 4 weeks on/2 weeks off schedule. Despite this treatment, he showed a rapid initial worsening of his symptoms, and 15 days later, he became bedridden because of leg weakness and somnolence [Karnofsky performance index (KPS) of 30]. He also became incontinent of urine and presented a new onset of severe bilateral deafness. Due to these reasons, the temozolomide treatment was discontinued, and the patient was referred to a hospice without further investigations.

In the following weeks, however, he showed remarkable improvements: the bladder incontinence disappeared, the deafness improved and he progressively regained strength of the lower extremities. Temozolomide was restarted at 100 mg daily (4 weeks on/2 weeks off). Two months after starting temozolomide treatment, the deafness had completely recovered and the patient had regained 13 kg. He was able to walk without assistance (KPS 70). One month later, the spine MRI was repeated and showed a complete resolution of the lesions (fig. 1c, d). After 4 months of temozolomide therapy, the patient resumed jogging and his hobby as a glider pilot (KPS 100). Temozolomide was discontinued after 6 months of therapy.

Four months later, however, the patient presented with new-onset hearing loss on the left side. Brain and spinal MRIs confirmed extensive LMC. The patient developed difficulties swallowing, thus temozolomide could not be restarted. Despite subsequent treatment with intrathecal liposomal cytarabine (Depocyt®), the patient required palliative care hospitalization and died from pneumonia within 3 months.
Discussion

Oral temozolomide and dacarbazine (i.v.) are alkylating agents with similar activity against systemic melanoma [5]. In contrast to dacarbazine and other drugs used against melanoma, temozolomide crosses the blood-brain barrier and has been shown to induce clinically relevant responses in patients with cerebral metastases of melanoma [6]. Knowledge of patients suffering from leptomeningeal melanomatosis is limited, as these patients are not included in clinical trials. A complete response was reported for a patient with LMC from melanoma treated with a combination of oral temozolomide and cisplatin i.v. [7]. In the present case, we observed a complete radiological response as well as a dramatic improvement in quality of life with a complete recovery of autonomy and social activities following treatment with temozolomide alone. Interestingly, this was achieved after a transient severe degradation, underlying the reversibility of neurological defects in such a condition. The schedule of 75 mg/m²/day (4 weeks on/2 weeks off) was selected to allow maximal exposition to the alkylating agent.

The encouraging clinical response reported here suggests that dose-intensified temozolomide might have significant activity in the treatment of leptomeningeal dissemination of melanoma and may be a valid treatment option for patients who have not been previously exposed to this agent. Moreover, this treatment regimen is extremely well tolerated and obviates the need for repeated intrathecal administrations of chemotherapeutic agents, which are often not well tolerated by patients who have significant co-morbidities due to their disease. As illustrated in this case, response to temozolomide may occur in a delayed manner, highlighting the importance of following temozolomide treatment long enough before determining that it is inefficient in a given patient.

Disclosure Statement

The authors have no conflicts of interest to declare.
**Fig. 1.** Gadolinium-enhanced MRI of the cervical (a, c) and lumbar (b, d) spine. Contrast-enhancing lesions (arrows) are seen at the time of diagnosis of LMC (a, b). After 3 months of temozolomide treatment, there is complete resolution of the lesions (c, d).
Fig. 2. Cytology of the CSF at the time of diagnosis. a HE staining. b Immunostaining against Melan-A.

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