VIA MEDICA

CASE REPORT

Łukasz Kwinta, Piotr J. Wysocki

Department of Clinical Oncology, Jagiellonian University-Medical College, Krakow, Poland

Strikingly high activity of metronomic chemotherapy in a patient with locally advanced, life-threatening cutaneous squamous-cell cancer — case report and discussion of the literature

Address for correspondence:
Prof. Piotr J. Wysocki, MD PhD
Department of Clinical Oncology,
Jagiellonian University Hospital
ul. Kopernika 50, 31–501 Kraków, Poland
phone: +48 12 351 6700
fax: +48 12 424 7180
e-mail: piotr.wysocki@uj.edu.pl

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ABSTRACT

The current treatment of choice in patients with advanced or metastatic squamous-cell carcinoma (SCC) of the skin is immunotherapy based on anti-PD1/L1 antibodies. For many years, there has been a consensus, that SCC of the skin is a chemorefractory neoplasm. However, despite a recent approval of checkpoint inhibitors for the treatment of cutaneous SCC, their extremely high cost makes them unavailable for many patients worldwide, and additionally, in many patients, their use may be contraindicated by patients' clinical conditions. This article provides strong arguments that optimized and well-matched chemotherapy still represents an active treatment option even in the era of novel therapies.

Key words: metronomic chemotherapy, skin squamous-cell carcinoma, skin cancer, cutaneous malignancies

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Introduction

Squamous-cell carcinoma (SCC) of the skin, originating in keratinocytes, is the second most common, non-melanocytic cutaneous malignancy after basal-cell carcinoma. The primary treatment modality in a locoregional disease is a wide resection with optional adjuvant radiotherapy. In the case of locally advanced or disseminated disease, the current systemic treatment is immunotherapy based on anti-PD-1/L1 antibodies [1, 2]. The very high costs of checkpoint inhibitors make these drugs unavailable for many patients worldwide. Still, even when immunotherapy is available, its use may be inappropriate in many cases of advanced, symptomatic SCC patients due to the risk of a rapid, immediately life-threatening progression of tumor lesions. The current article presents a clinical case of a patient with severely symptomatic, locally advanced skin SCC in whom immunotherapy was contraindicated and who experienced a complete response with multidrug metronomic chemotherapy. This article provides strong arguments that optimized and well-matched chemotherapy still represents a promising treatment option even in the era of novel therapies.

Case report

A 75-year-old patient with a massively advanced SCC of the skin penetrating deeply in the direction of the spinal bulb (Fig. 1A) was admitted to the Oncology Department of the University Hospital in Krakow

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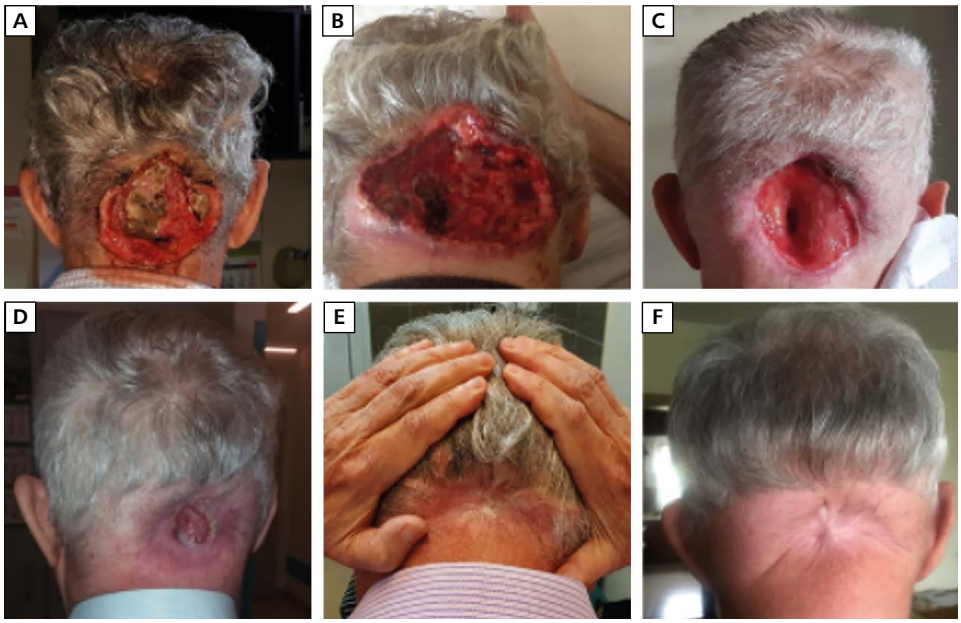

Figure 1. Stages of response of locally advanced squamous-cell carcinoma of the skin to metronomic chemotherapy; **A.** Before initiation; **B.** Progression during MCC (Methotrexate, Cyclophosphamide, Capecitabine) regimen; **C.** One month after initiation of oral metronomic chemotherapy (CPC) regimen; **D.** At the time of initiation of de-escalated CPC-based chemotherapy; **E.** Complete clinical response at the time of initiation of consolidative radiotherapy; **F.** Six months after consolidative radiotherapy

in August 2019. The diagnosis was established 2 months earlier, but due to the patient's condition and the size and location of the lesion, he was not qualified for a local and systemic treatment. There were objective contraindications for immunotherapy because of the risk that a paradoxical progression might result in life-threatening spine compression. Chemotherapy was not offered because of the patient's poor performance status [Eastern Cooperative Oncology Group (ECOG) = 2] and bleeding risk.

Magnetic resonance imaging (MRI) performed one month before admission revealed massive infiltration of the skin and subcutaneous tissues of the occipital and neck regions penetrating the intermuscular fascia (Fig. 2A–B). Before initiation of treatment, the patient complained of severe pain radiating to the head and neck. The ulcerated crater-like lesion in the skin, 8 cm in diameter, penetrated deeply into subcutaneous tissues and was filled with necrotic, inflammatory masses that bled intensively upon contact (Fig. 1B). The patient's relatively poor condition and severe symptoms (inability to remain in a lying position) did not allow for performing baseline computed tomography (CT) or MRI. Ultrasound examination of the abdomen and chest radiography revealed no signs of dissemination. Additional pathomorphological verification showed no estrogen, progesterone, or androgen receptor expression and a low proliferation rate (Ki67 = 9.5%). Considering the patient's symptoms, performance status, and an imminent threat to his life in case of further disease progression,

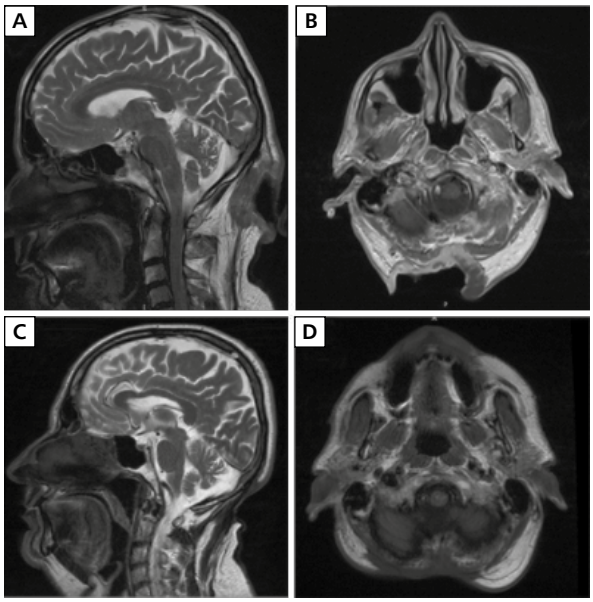

Figure 2. Magnetic resonance scans of the head and neck region; **A, B.** Before initiation of metronomic chemotherapy; **C, D.** At the end of chemotherapy

he was started on metronomic chemotherapy based on an all-oral MCC (Methotrexate, Cyclophosphamide, Capecitabine) — Methotrexate 5 mg per os (p.o.), administered twice a week, Cyclophosphamide 50 mg p.o. q1d, and Capecitabine 500 mg p.o. tid.

Four weeks later, further, however subjectively less dynamic, clinical progression occurred. The patient complained of increasing pain, weight loss, and neurological symptoms of paresthesia in the lower and upper limbs. The paresthesia most likely resulted from the penetration neoplastic of the lesion into the cerebellum and spinal bulb (Fig. 2B). Therefore, an intensified intravenous/oral metronomic chemotherapy (CPC) regimen was initiated. In October 2019, the patient started on cisplatin 25 mg/m^2 intravenous (i.v.) and paclitaxel 50 mg/m^2 *i.v.* (administered on days 1, 8, and 15, repeated every 28 days) in combination with capecitabine (500 mg p.o. tid).

Within the next 2 weeks, the modified metronomic treatment resulted in a clinically significant reduction of pain and a gradual decrease in the lesion diameter. After 1 month of treatment with the CPC regimen, signs of response were observed (Fig. 1C). Initially, chemotherapy was associated with increased bleeding from the wound, but after 1 month, the bleeding subsided. Relief in pain and neurological symptoms was also observed. The patient discontinued opioids before the end of the second month of the CPC treatment. After 7 months of intensive (weekly) chemotherapy, when a major response was determined, the patient requested longer treatment intervals due to personal reasons. He continued to receive intravenous chemotherapy at 2-weekly intervals (at initial doses) and capecitabine daily (500 mg p.o. tid). Since then, the lesion has remained clinically stable (Fig. 1D). Magnetic resonance imaging done in August 2020 showed complete regression of the neoplastic lesion (Fig. 2C–D). Chemotherapy was administered for 15 months until a clinical complete response was confirmed (Fig. 1E). Considering the treatment benefit and emerging signs of ototoxicity (Grade 1 hearing loss from January 2021), systemic treatment was stopped entirely, and the patient was scheduled for consolidation radiotherapy, and currently, 6 months later, remains in observation and in complete remission (Fig. 1F). The long-term treatment with multidrug metronomic chemotherapy was tolerated very well. The administration of chemotherapy had to be postponed only twice due to Grade 2 neutropenia.

Discussion

Locally advanced or disseminated SCC of the skin is rare. The scarce data regarding the efficacy of classical systemic therapies in these clinical conditions come from small and retrospective studies or case series reports. The primary cytotoxic agents used to treat skin SCC are platinum compounds (mainly cisplatin), and additional drugs are taxoids, fluoropyrimidines, or bleomycin used alone or in combination. Recently, immune checkpoint inhibitors (cemiplimab and pembrolizumab) have been approved for the treatment of patients with advanced/metastatic skin SCC [1, 2]. In a pivotal phase I/II clinical study conducted in advanced/metastatic skin SCC patients, administration of cemiplimab was associated with a high rate of long-lasting objective responses (approximately 50%) [1]. However, complete responses (7%) occurred only in metastatic SCC patients, and 12–19% of patients failed to respond. Additionally, approximately 20% of patients progressed despite the initial benefit from immunotherapy. Another drug, pembrolizumab, which achieved 34% of objective responses (4% complete responses) was inactive in more than 26% of patients with skin SCC.[2] While considering immunotherapy, physicians must remember that despite its significant activity, many patients with advanced, symptomatic, or locally advanced tumors may not benefit from this therapy and experience early progression (sometimes even hyperprogression). In our patient, due to the highly symptomatic disease and life-threatening clinical conditions, the use of immunotherapy was contraindicated, and the only treatment option that remained was chemotherapy.

The activity of chemotherapy in SCC of the skin is modest at best. In a retrospective analysis of 19 patients (13 with locally advanced and 6 with metastatic SCC), monotherapy (paclitaxel, cisplatin, or carboplatin) led to 44% of objective responses while multidrug cisplatin-based regimens to up to 53% [3]. Median progression-free survival (PFS) was 5.5 months and median overall survival (OS) was 10.9 months. Still, no significant differences in PFS and OS were found between patients receiving single- or multidrug regimens. Another study evaluated combined chemotherapy (cisplatin, fluorouracil, and bleomycin) in 13 patients with locally-advanced SCC of the skin [4]. Such aggressive multidrug chemotherapy led to 30% of complete responses at the cost of substantial toxicity in more than 40% of patients. Another highly toxic chemotherapy regimen [weekly multi-agent chemotherapy CMF-b (Cyclophosphamide, Methotrexate, Fluorouracil, Bleomycin)] was evaluated in 26 patients with surgery-ineligible SCC and basal-cell carcinomas of the skin [5]. The treatment was associated with objective responses in 61.5% of patients, with 27% of complete and 34% of partial responses, but the median duration of response was only 6.1 months.

The available data on systemic therapies of advanced/metastatic SCC of the skin, albeit of low quality, demonstrate that treating symptomatic, usually elderly, patients represents a considerable challenge. Immunotherapy with checkpoint inhibitors is currently the treatment of choice in advanced/metastatic SCC of the skin. Still, its use may be significantly restricted in

patients with severe symptoms or a high disease burden. Additionally, due to their cost and reimbursement issues, the availability of immunotherapies represents another socially significant problem.

Metronomic chemotherapy is a reasonable therapeutic approach in many patients with advanced, non-rapidly proliferating cancers, especially those who are elderly or have significant comorbidities [6–12]. The oral-intravenous approach presented in this article represents smart combined chemotherapy designed to activate all possible mechanisms of the cytotoxic drugs used. These mechanisms engage not only the standard antiproliferative activity of cytotoxic agents but also their antiangiogenic and immunostimulatory potential induced by continuous low-dose administration. Those targeted therapeutic properties of metronomic chemotherapy are considered an alternative in many low-income countries with restricted access to targeted agents. However, as shown in our patient's case, this approach may still represent a treatment of choice even if some novel advanced therapies are available. Based on the literature and the presented case report, there is no doubt that a skillful adjustment of chemotherapy to biological properties of particular tumors allows for achieving significant clinical benefits, with minimized risk of disease progression or severe adverse reactions. In the era of the COVID-19 pandemic, metronomic chemotherapy, with its efficacy and excellent safety profile, represents an extremely convenient and safe treatment option [7, 13].

Conflict of interest

Authors declare no conflict of interest.

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