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Review article

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Merkel cell carcinoma (MCC) – neuroendocrine skin cancer

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Merkel cell carcinoma (MCC) is a rarely occurring skin cancer of high malignancy. It develops, most probably, from the neuroendocrine cells (Merkel's cells). The most frequent location of this cancer is the skin of the head and neck (44–48% of cases), and then in the skin of the upper limbs (about 19% of cases) and then the lower limbs (16–20% of cases). The aetiology of this cancer is unknown, yet some role in its pathogenesis is played by ultraviolet light and immunosuppression. The basis of therapy in cases with locoregional spread is surgical intervention, whilst in more advanced cases, an effective systemic treatment is possible with the use of molecularly targeted therapies. This paper presents the current treatment possibilities in patients with Merkel cell carcinoma.

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Key words: Merkel cell carcinoma, diagnostics, surgical treatment, systemic treatment

Introduction

Merkel cell carcinoma (MCC) is a rarely occurring skin cancer of high malignancy. It develops, most probably, from the neuroendocrine cells (Merkel's cells) [1, 2].

The incidence of MCC is low, evaluated to be 0.25––0.32/100 000 people per year. The prevalence is higher among men than women (at a ratio of 1.5:1). This cancer is markedly more common in representatives of the white race than in other races. The risk of developing MCC increases with age – the frequency of MCC in patients below 50 years of age is very low. The most frequent location of this cancer is the skin of the head and neck (44–48% of cases), the skin of the upper limbs (about 19% of cases and then the lower limbs (16–20% of cases) [3, 4]. Merkel cell carcinoma very rarely develops within the mucous membranes. There are also patients in whom – though with a lack of detectable primary focus – the metastases of Merkel cell carcinoma are found in the lymph nodes [5]. According to some findings, such cases may account for 10%–15% of all MCC cases. Observational studies in the USA population seem to suggest that the incidence of Merkel cell carcinoma is increasing, which may be connected with the ageing population and be an outcome of developments in histopathological diagnostics [6].

Aetiology

The aetiology of this cancer is unknown though there are well identified factors which predispose for MCC. These factors comprise first and foremost:

- Exposure to ultraviolet irradiation (UV) – whether natural or artificial, e.g. after treatment for psoriasis with the use of phototherapy and psolaren ultraviolet A – PUVA) [7, 8];
- Immunocompromising diseases, such as:
  a) HIV/AIDS infection (the risk of developing MMC is increased 11-fold) [9],
  b) immunosuppression after an organ transplant (the risk of developing MMC is increased 5-fold) [10, 11],
  c) chronic lymphocytic leukaemia;
- Some viral infections, with the most significant being a *polyoma* infection – the type characteristic for MCC: Merkel cell polyomavirus (MCPyV) [12, 13]. The role of MCPyV in the pathogenesis of MCC is unclear. Viral DNA is detected in 60–80% people affected with MCC. At the same time,

in people with the confirmed presence of the virus, longer overall survival is observed in comparison with the group of patients without the viral infection [12, 14].

Diagnostics

Merkel cell carcinoma (MCC) most frequently takes the form of a relatively rapidly expanding tumour or solid infiltration on the skin, often of a red to violet colour. Ulceration is rare. Sometimes the tumour spreads quickly through the pathways of local lymphatic vessels, which in turn leads to the development of satellite foci. The tumour is not usually accompanied by any disorders – it is painless in the majority of cases [15]. This unspecific clinical picture has the effect that MCC is rarely suspected before the result of a histopathological assessment of material from an excisional biopsy or specimen.

In English-language publications, a mnemotechnical acronym has been proposed to facilitate MCC diagnostics – AEIOU:

A – asymptomatic;
E – expanding rapidly;
I – immunosuppressed;
O – older than 50 years;
U – UV-exposed skin.

Only 7% of MCC patients meet all the above criteria, but in about 90% of patients, at least 3 of these criteria can be found [15].

The clinical picture and a short interview suggestive of a lesion of a malignant nature, may be an indication for an excisional biopsy performed in accordance with generally binding principles. Microscopic assessment of the excised tumour allows for diagnosis. The pathological diagnosis is facilitated by immunohistochemistry. The histopathological image of the lesion shows a small cell cancer (often the expression of cytokeratin 20 and neuroendocrine markers and a lack of TTF-1 expression characteristic of small cell lung cancer [SCLC] are observed; PD-L1 expression is present in about 50% of cases).

In order to evaluate the stage of the disease in the cases where a Merkel cell carcinoma tissue pattern is found, it is recommended to perform a physical examination and imaging diagnostics. Depending on individual indications, these would be an X-ray, computed tomography (CT), magnetic resonance (MR), possibly in conjunction with pathological or cytological diagnostics (fine needle aspiration biopsy) of the suspicious foci.

In some cases, where the histopathological diagnosis is doubtful and there is a suspicion of an extra-dermal primary focus of the cancer (skin metastases of the tumours other than MCC, e.g. SCLC), there may be some indications to expand the diagnostics process with positron-emission tomography (PET) in conjunction with CT.

Clinical stages, prognosis

Currently the eighth edition of the tumour classification, as established by the American Joint Committee on Cancer (AJCC) is in use. This classification is based on typical TNM criteria (tumour-node-metastases) (table I and II) [5, 16–18]. It seems, however, that the factors with the largest prognostic value are the primary tumour size, the presence of metastases at the moment of diagnosis and the scope of the involvement of lymph nodes.

The ten-year overall survival in MCC patients is estimated to be 65% in women and 50.5% in men (57% on average for

Table I. Classification of MCC stages (2017)

Primary tumour (T)	
TX	Primary tumour not possible for evaluation
T0	No presence of primary tumour (e.g. node metastases with unknow primary focus)
Tis	cancer *in situ*
T1	Maximum tumour diameter up to 2 cm
T2	Tumour diameter above 2 cm up to 5 cm inclusive
T3	Maximum tumour diameter above 5 cm
T4	Tumour infiltration to the bones, muscles, fascia or cartilage
Regional lymph nodes (N)	
NX	Regional lymph nodes not possible for evaluation
N0	No metastases in regional lymph nodes
N1	Metastases in regional lymph node(s)
N1a (sn)	Micro-metastases (detected in the sentinel node biopsy)
N1a	Clinically not detectable metastasis found in lymphadenectomy
N1b	Macro-metastases (found in clinical or radiological assessment), confirmed in microscopic evaluation
N2	Metastases *in transit* without the metastases in regional lymph nodes
N3	Metastases *in transit* with the metastases in regional lymph nodes
Distant metastases (M)	
M0	No metastases
M1	Metastases in distant organs (other than regional lymph nodes)
M1a	Metastases in the skin, subcutaneous tissue and lymph nodes
M1b	Lung metastases
M1c	Other locations of metastases

Table II. Pathological stages/prognostic groups

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2–T3	N0	M0
IIB	T4	N0	M0
IIIA	T0	N1b	M0
IIIA	Each T	N1a (sn)/ N1a	M0
IIIB	Each T	N1b–N3	M0
IV	Each T	Each N	M1

all patients). Depending on the size of the primary tumour, the 10-year survival rate is as follows:

- for tumours with a 2 cm diameter or smaller – 61%
- larger than 2 cm – only 39% [5]

5-year survival is the following:

- 37% – for patients with locoregional spread (stage IIIb)
- 16% – for patients with distant metastases [19].

Treatment

The basis of therapy in cases with a locoregional spread is surgical intervention. The treatment of an MCC should be carried out in highly specialised centres [17, 20, 21].

Clinical stage I and II

Where there is a lack of detectable metastases in the regional lymph nodes, a sentinel node biopsy should be considered with a wide scar excision (up to a margin of at least 1–2 cm). This is prompted by the observation that metastases in the sentinel nodes occur in 25–35% of patients even when clinical symptoms of metastases are not present. The risk of developing micro-metastases increases significantly in patients with a primary focus with a diameter measuring 1cm or more [22, 23].

The majority of recommendations suggest that local surgical treatment should be combined with radiotherapy, although the efficiency of such an approach has not been confirmed in randomised trials. However, the recently published results of a meta-analysis of the available observations suggest that radiotherapy slightly improves the overall survival rate and significantly affects the locoregional control of the tumour. The results of the meta-analysis show that patients with an MCC in stage T2 or later benefit from the combination of surgery with radiotherapy [24].

Clinical stage III

The presence of metastases in regional lymph nodes (both micro- and macro-metastases; stage III) is an indication of the resection of the regional lymph nodes.

In spite of the lack of evidence coming from studies with patient randomisation, the majority of retrospective analyses point to an improvement of loco-regional control and patient survival after the application of adjuvant radiotherapy to the bed created after the resection of regional lymph nodes (at a dose of 50–60 Gy) [25, 26].

Some authors postulate that in patients with a massive involvement of the lymph nodes, chemotherapy should also be considered. However, no typical systemic therapy in this group of patients has been established – the treatment can be carried out both preoperatively and postoperatively. In some centres, lymphadenectomy in these patients is performed between chemotherapy cycles. The published data do not allow, however, for a definitive conclusion as to whether systemic therapy affects the improvement of overall survival in this group [26–28].

Preliminary results from the application of checkpoint inhibitors in preoperative treatment of an MCC seem to be promising. In 2018, the results of a I/II phase trial of the use of nivolumab in neoadjuvant treatment of MCC patients in stage IIa–IV (CheckMate 358) were published. The trail comprised 29 adult patients who had not been previously systemically treated for an MCC. In the majority of patients, the presence of polyoma virus (MCPyV; 71.4%) was found. The PD-L1 expression was established in 20 patients and in 30% of them the expression was on the level of at least 1%. The patients received a nivolumab infusion at a dose of 240 mg on day 1 and 15 (counting from the commencement of therapy), and then on day 29, surgery was performed. Out of 27 patients who underwent surgery, 9 received post-operative radiotherapy and 1 patient received nivolumab for one year on account of the progression of the disease. After a median follow-up period of 67.1 weeks, in 40% of the 25 patients, radiological assessment revealed a decrease of the lesions by about 30%. No correlation between the treatment response and MCPyV status and PD-L1 expression was found. Although the radiological assessment revealed only one complete response, in the pathological assessment, a complete pathological response was found in 47% patients and a major pathological response (≤10% of live tumour cells) in 18% patients. In some patients, the response which was achieved allowed for surgery with a smaller scope. At the same time, no median progression free survival (PFS) or median overall survival (OS) were gained. The rates of progression free survival after 6 and 12 months were 92.1 and 72.6% respectively. The survival rates after 18 and 24 months were 100 and 75% respectively. In none of the patients with complete or major pathological response was disease recurrence observed.

The drug safety profile was compliant with the results seen in other clinical trials. No adverse events of grade 5 or severe were observed. In none of the patients qualified for surgical intervention was it necessary to postpone the surgery on account of poor tolerance for the systemic treatment [29].

Currently there is a multi-centre, phase III, double blinded, placebo-controlled clinical trial being carried out with the objective to evaluate the efficacy of avelumab in the adjuvant treatment of MCC patients after surgical treatment (with or without radiotherapy) with clinically confirmed metastases in regional lymph nodes (NCT03271372). The patients are randomised (ratio 1:1) either to a group receiving avelumab at a dose of 10 mg/kg of body mass or to a placebo group. The primary endpoint is recurrence free survival [30].

Clinical stage IV

In cases of advanced disease, the treatment is palliative. In patients who are in a satisfactory condition, palliative chemotherapy might be considered although there is no data which could confirm the effect of such treatment on overall survival. Additionally, the justification for immunotherapy sho-

uld be evaluated [17, 31] – provided that it is available – as there are data pointing to its efficacy. On account of the high activity of immune system checkpoint inhibitors (anti-PD-1 and anti-PD-L1) in the treatment of metastatic MCC, current recommendations suggest the application of these drugs as treatment of choice (a fact which has been confirmed by phase II clinical trials) [32].

Many observations point to the chemosensitivity of MCC (although the response does not exceed 8–10 months and the rate of long-term overall survival stands at 0–18%). The most frequently used therapeutic regimes are chemotherapy with cisplatin, doxorubicin and vincristine or etoposide as well as 5-fluorouracil or cyclophosphamide. In cases where it is justified, palliative surgical interventions and/or radiotherapy may also be applied.

In 2019, the results of a retrospective analysis of treatment patterns was applied to patients with newly diagnosed MCC, treated between October 2013 and January 2018. Out of 120 patients treated systemically within the first line of treatment, 17%, 45% and 38% patients were treated with checkpoint inhibitors, chemotherapy applied according to the NCCN guidelines or another type of chemotherapy respectively. The most frequently used chemotherapy patterns were carboplatin with etoposide and cisplatin with etoposide. Only 33% patients systemically treated in the first line commenced the second line of treatment [33].

Moreover, the results of clinical studies into the use of avelumab, pembrolizumab and nivolumab in the treatment of advanced MCC have been published.

A single-arm second phase clinical trial, JAVELIN Merkel 200, showed the efficacy of avelumab in the treatment of MCC with metastases after the failure of systemic chemotherapy; avelumab was administered at a dose of 10 mg/kg of body mass intravenously every two weeks until the moment of progression or unacceptable toxicity. The objective response rate (ORR) was 31.8% (95% confidence interval (CI): 21.9–43.1%; 28 patients), including 8 complete responses (9%) and 20 partial responses (23%). Additionally, in 9 patients (10%) disease stabilisation was observed [34]. The treatment responses had a lasting effect and, at the moment of analysis, they persisted in 23 (82%) patients. The length of the response was at least 6 months in 92% of cases. The median PFS was 2.7 months (95% CI: 1.4–6.9), and the rate of patients free from disease progression after 6 months was 40%. The PFS curves reached *plateau*. The survival rate after 6 months was 69% (95% CI: 58–78), and the median OS – 11.3 months (95% CI: 7.5–14.0). Objective responses were obtained in the following patients:

- 20 out of 58 patients (34.5%) with PD-L1 expression,
- 3 out of 16 patients (18.8%) PD-L1 (–),
- 12 out of 46 patients (26.1%) MCPyV (+),
- 11 out of 31 patients (35.5%) MCPyV (–).

More responses were obtained in patients who had previously undergone only one line of treatment. Avelumab was generally well tolerated. Treatment related adverse events occurred in 62 (70%) out of 88 patients. Updated results with median follow-up periods of 18 months and 24 months published in 2018, confirm the efficacy of avelumab for this indication. On the basis of an analysis of the data from 88 patients followed up for 29.2 months (24.8–38.1) it was observed that the median OS was 12.6 months (95% CI: 7.5–17.1), with the 2-year survival rate being 36% (50% survival after 1 and 39% after 1.5 years). The median treatment period was 3.9 months (0.5–36.3). The rate of confirmed ORR was 33.0% (95% CI: 23.3–43.8; CR observed in 11.4% patients) and this remained on the same level as in the case of the analyses carried out after one year and 1.5 years of follow-up. The median response period was not reached (2.8–31.8 months; 95% CI: 18.0 – not reached). The long-term responses to avelumab treatment determine stable PFS values in evaluations after 1 year of observation (29%), after 1.5 years (29%) and after 2 years of follow-up (26%). Clinical activity persisted irrespectively of PD-L1 expression status and the presence of polyoma virus. The tolerance profile of avelumab was consistent with those already existant. In 67 patients (76.1%) treatment related adverse events were observed and in 10 patients (11.4%) they were at least 3 grade. In 20 patients (22.7%) adverse events related to immunological activity of avelumab were observed. No deaths connected with the treatment occurred [35, 36].

The second phase trial, JAVELIN Merkel 200, also resulted in the registration for the first line of treatment of advanced MCC. The data concerning the survival of these patients, published in 2018, point to a mean survival rate of 49.9 months (6.3; 179.4) with the one year and five year survival rates being 66% and 23% respectively [37]. So far no predictive factors of avelumab treatment response of MCC patients have been established [38].

In 2017, during the annual conference of the American Society of Clinical Oncology (ASCO), the preliminary results of part of the second phase trial with the use of avelumab (JAVELIN Merkel 200) in the first line of treatment of advanced MCC were presented [39]. In 16 patients, after a follow-up period of at least 3 months, the response rate was 62.5% (in 10 patients 3 complete remissions and 7 partial remissions were observed), and all these responses persisted at the moment of the last evaluation. The updated results of part B of this trial confirmed that 77.8% (14 out of 18) treatment responses persisted and the response duration in 83% cases was longer than 6 months (95% CI: 46–96%) [40]. In 29 patients, the safety of the therapy was evaluated: adverse events with minimum toxicity grade 3 occurred in 5 patients (17.2%), and this was the reason for the termination of the treatment (2 patients developed reactions related to the administration of the drug, such as increased activity of aspartate aminotransferase and alanine aminotransferase, cholangitis, paraneoplastic syndrome and gait disorders). According to recently updated analysis, in 8 patients in total there were grade 3 adverse events related to the immunology system (20.5%).

A second phase clinical trial published in 2016 showed the efficacy of pembrolizumab (anti-PD-1 antibody) in the treatment of the stage IIIB–IVC MCC patients, who were systemic treatment naïve [41]. This was a multi-centre clinical trial (Cancer Immunotherapy Trials Network-09/Keynote-017), which enrolled 50 patients with advanced MCC. They received pembrolizumab at a dose of 2 mg/kg of body mass every 3 weeks for up to 2 years. The median age of the subjects was 70.5 years. In 64% the tumour was MCPyV(+). The efficacy evaluation was performed on the basis of RECIST 1.1. criteria; the ORR totalled 56% (CR 24%, PR 32%; 95% CI: 41.3–70.0%): the ORR in the patients in the group MCPyV(+) was 59%, whilst in those in the group MCPyV(–) it was 53%, with a median follow-up of 14.9 months (range 0.4–36.4 months). Among the 28 patients in whom a treatment response was observed, the median response duration was not reached (range 5.9–34.5 months). The PFS ratio after 24 months was 48.3% with a median PFS of 16.8 months, whilst OS rate after 24 months was 68.7%, and the median OS was not reached. The presence of polyoma virus did not correlate with ORR, PFS or OS. Some trend for better results concerning PFS and OS was observed in patients with PD-L1 expression. Treatment related adverse events ≥G3 were found in 28% of patients (14 out of 50) and in 14% (7 out of 50) these events required the termination of the treatment. One treatment related death occurred [42].

Similarly, in the avelumab trial, a tendency towards greater treatment response was observed where the number of previous treatment lines was smaller. This shows (taking into consideration the pembrolizumab trials), that immunotherapy in MCC should be the treatment of choice in the first line of therapy. In all the presented trials, the responses were found in both MCPyV-positive and negative patients, and, as was confirmed, this type of treatment may also be applied to elderly patients (a fact which is vital given that this disease develops mostly among people of advanced age).

Currently, immunotherapy with anti-PD-1/anti-PD-L1, in accordance with Polish and international recommendations, makes for standard systemic treatment in patients with unresectable/metastatic MCC [32, 43], and avelumab, registered for this indication in the European Union, is available in Poland as part of the Emergency Access to Therapy programme (Ratunkowy Dostęp Terapii Lekowej) in conjunction with a positive opinion on the part of AOTMiT (the Agency for Health Technology Assessment and Tariff System).

Additionally, preliminary results of the first and second phase trials with nivolumab administered in a group of 22 patients with MCC. In these people, the ORR rate was 68% after the 26-week follow-up period (with a scope of 5–35 weeks) and it was slightly larger in patients who had not been systemically treated previously (71%, n = 14), in comparison with those who had been previously treated (63%, 1 or 2 lines of previous treatment, n = 8) [44].

The treatment of local relapses and recurrences in regional lymph nodes

The most frequent recurrence form is a local relapse. This affects about 30% of patients treated surgically (postoperative radiotherapy decreases this rate to about 11%) [45].

Local relapses may be treated like a primary MCC with correct reference to the clinical stage (I–III). If possible, the tumour foci should be resected with a margin of healthy tissues, with adjuvant radiotherapy, provided that this was not applied for the treatment of the primary focus. Disease recurrence makes for a bad prognosis, and for this reason systemic adjuvant treatment should also be considered even though there still is no evidence for its effectiveness.

Conflict of interests: non declared

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