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REVIEW

Merkel Cell Carcinoma: Therapeutic Update and Emerging Therapies

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ABSTRACT

Merkel cell carcinoma (MCC) is a rare but highly aggressive neuroendocrine skin cancer whose incidence has almost doubled in recent decades. Risk factors for MCC include age > 65 years, immunosuppression, sun exposure and infection by Merkel cell polyomavirus. MCC usually presents as rapidly growing, firm, red to violaceous nodule localized on the sun-exposed skin. Surgery followed by radiation therapy is considered to be the first-line treatment for primary or loco-regional MCC in order to prevent recurrences and lymph node metastasis, while chemotherapy has always been used to treat advanced forms. However, responses to chemotherapy are mostly of short duration, and the associated clinical benefit on overall survival is still unclear. The use of checkpoint inhibitors (CPIs) has shown good results in the treatment of advanced MCC and, consequently, CPIs are considered emerging immunotherapeutic options for these patients, although there are still no standardized treatments for patients with metastatic disease. Here we present a complete overview of the different possibilities for the treatment of MCC according to the stage of the disease, focusing on the emerging immunotherapies used for treating advanced MCC.

Keywords: Avelumab; Chemotherapy; Immunotherapy; Immune checkpoint inhibitor; Merkel, skin cancer; Surgery

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INTRODUCTION

Merkel cell carcinoma (MCC) is a rare but highly aggressive neuroendocrine skin cancer associated with frequent recurrences, metastasis and highly mortality rate [1–4]. The incidence of MCC in the USA almost doubled between 2000 and 2013 and is expected to exceed 3000 cases per year by 2025, with similar increases expected in Australia and many European countries [5–8]. This increase may be related to an aging population and improvement in diagnostic recognition. The risk factors include age > 65 years [9], immunosuppression [10–12], sun exposure and infection by Merkel cell polyomavirus (MCPyV) [13]. MCPyV infection has been detected in almost 80% of MCC cases [14–16], whereas the other 20% with no detectable MCPyV levels were triggered by ultraviolet-mediated mutations [17, 18]. MCC

classically presents as a rapidly growing, firm, red to violaceous nodule on sun-exposed skin, including the head–neck region and limbs, of an elderly, fair-skin individual [19–22]. However, up to 15% of patients will present with a tumor-positive lymph node without a visible cutaneous manifestation; these cases probably represent metastatic disease with regression of the primary skin tumor. Histopathological and immunohistochemical examinations (including chromogranin A, and/or synaptophysin and cytokeratin-20) are necessary to confirm the diagnosis [23–26]. A wide local excision followed by radiation therapy (RT) is considered to be the first-line treatment for primary or loco-regional MCC in order to prevent recurrences at the primary site and lymph node metastasis (stage I and II), while cytotoxic chemotherapy with platinum-based regimens, etoposide, anthracyclines and taxanes, in different combinations or alone, has always been used to treat patients with metastatic MCC [26, 27]. However, recent advances in the understanding of the biology of MCC, for example the discovery of MCPyV, have created opportunities for the development of novel therapeutic strategies that may improve treatment efficacy. The use of checkpoint inhibitors (CPIs) has shown good results in the treatment of advanced MCC and, consequently, CPIs are considered to be emerging immunotherapeutic options for these patients [28]. Since MCC, especially in its advanced form, is frequently refractory to adequate systemic treatment, a long-term treatment is often required to control the burden of the disease, prevent flare-ups and achieve better patient quality of life outcomes. This has led to large variations in systemic treatment approaches worldwide; this situation is further exacerbated by the lack of international standardized guidelines [13, 29].

In this review, we analyze the existing literature and present a complete overview of the different possibilities for the treatment of MCC according to the stage of the disease, focusing on the emerging immunotherapies used to treat advanced MCC.

METHODS

We searched the English-language literature on the management of MCC and its treatment in the following databases through to 20 December 2018: PubMed, Embase, The Cochrane Library, Google Scholar, EBSCO and Scopus. The following key words were used: "Merkel cell carcinoma," "Merkel," "surgery," "radiotherapy," "immunotherapy," "avelumab," "ipilimumab," "targeted therapy," "advanced Merkel cell carcinoma." All of the published articles identified (case report, case series, prospective and retrospective studies, clinical trials, reviews, guidelines and consensus) were reviewed to provide a complete overview of and detailed data on new targeted therapies, which represent an exciting perspective for the management of advanced forms of MCC.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Current Treatment Options in MCC

The choice of treatment depends on the tumor characteristics, such as the stage at presentation, regional lymph node involvement, location of the disease, comorbidities and performance status of the patient [29–31]. Current treatment strategies that incorporate surgery and/or radiotherapy achieve high rates of locoregional control, but they are commonly associated with the development of distant metastases. Chemotherapy has demonstrated limited efficacy in the treatment of metastatic disease, but advances in immunotherapeutics are likely to have a major impact on the management and outcomes of MCC. As treatment options for the loco-regional form have already been standardized, there are no therapeutic agents specifically approved for the treatment of the advanced form of MCC, and treatment choice is often based on data available from retrospective series and prospective randomized controlled trials [32]. In the metastatic setting, chemotherapy has limited efficacy, but advances in immunotherapeutics are likely to have a

major impact on the management and outcomes of MCC.

Locoregional Primary MCC

Surgery

Surgery has typically been the first-line treatment for patients with locoregional primary MCC. However, just how much of the surrounding normal-appearing skin should be excised around the tumor during surgery is still controversial [32, 33]. Complete surgical excision, with the goal of establishing clear margins, is the mainstay to treat local MCC. Although surgical margins have not yet been defined, a wide excision with 1 to 3 cm of clinically free margins is generally recommended, regardless of tumor size [34]. A correlation between margin size and the recurrence risk has not been established, with some studies suggesting that wide margins of 2–3 cm are associated with a reduction of recurrence risk [35–37] and others showing no difference in recurrence risk with margins that are > 1 cm [38]. According to the current National Comprehensive Cancer Network (NCCN) guidelines, for local disease excision should be done with margins of 1–2 cm and down to the fascia or periosteum [26]. The recurrence risk of MCC after a wide excision ranges from 25 to 40% [35, 39, 40]. When tissue sparing is critical, due to the anatomic location of the tumor with complete peripheral and deep margin control, Mohs micrographic surgery (MMS) and modified Mohs surgery are also considered [41–43]. Several retrospective studies have demonstrated Mohs surgery to be effective, although prospective studies comparing MMS to wide local excision have not been performed [44]. Some authors report that MMS is related to an increased risk of developing in-transit metastases. Patients with clinical node-positive disease should undergo complete lymph node dissection (CLND) followed by radiotherapy on a case-by-case basis [45]. For clinical node-negative cases, sentinel lymph node biopsy (SLNB) is required [29], concurrent with primary MCC excision, in order to define microscopic lymph node status [46]. If the SLNB is positive, patients should undergo lymph node dissection and/or RT, as MCC is responsive to the latter [47, 48].

Radiotherapy

Merkel cell carcinoma is a radiosensitive tumor [49], and RT should be considered either as adjuvant treatment to surgery or as palliative treatment for inoperable cases of MCC. In some studies, adjuvant RT was recommended for patients with loco-regional tumor in order to reduce the recurrence rate, although the impact on the overall survival is still unclear [50–52]. However, the outcomes of radiation monotherapy may be inferior to those of complete surgical resection [49, 52, 53]. There are few published studies reporting the outcomes of RT and its effects on MCC relapse and disease-specific survival. A retrospective study of 57 inoperable patients treated with localized RT reported an overall survival rate at 5 years of 39% [51]; similar results have been reported in a retrospective study involving 43 patients in which an overall survival rate of 37% was reported [52]. The NCCN guidelines recommend doses of 60–66 Gy for curative-intent radiation, with a wide treatment margin (5 cm) around the primary site [48]. Radiation doses to the primary site after surgical resection should range from 50 to 60 Gy depending on the presence or absence of microscopically positive margins [33, 48].

Localized MCC Adjuvant RT to the tumor bed for local control after wide excision may be associated with lower recurrences [54], although the benefits to overall survival remain controversial. An analysis of 185 patients with localized MCC and margin-negative excision found that adjuvant radiation to the surgical bed did not improve the rate of local control [38]. Conversely, other studies have found that adjuvant radiation in early-stage MCC is beneficial and should be administered expeditiously after surgery [55–57]. In 2016, Bhatia et al. conducted a retrospective analysis on 6908 patients with MCC treated with surgery and adjuvant RT. For localized MCC (stage I: 3369 patients, stage II: 1474 patients), surgery plus adjuvant RT was associated with statistically significant better overall survival than with

surgery alone in the multivariable analyses (stage I: hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.64–0.80, $P < 0.001$; stage II: HR 0.77, 95% CI 0.66–0.89, $P < 0.001$). In patients with regional nodal metastases (stage III: 2065 patients), neither adjuvant RT nor chemotherapy was associated with statistically significant improved or worsened overall survival [58]. The standard practice is to consider radiation to the primary site alone if the SLNB is negative, but to include the nodal basin if the SLNB is positive [59].

MCC with Nodal and Metastatic Disease

Although most studies lack standardized treatment protocols for patients with clinically or pathologically positive nodal disease, standard treatment options include complete lymph node dissection, definitive nodal radiation or a combination of the two [60–63].Two independent studies comparing these two treatment options found no difference in terms of regional recurrence or overall survival between groups treated with CLND, definitive RT or combination therapy. The NCCN guidelines recommend adjuvant radiation to the draining nodal basin after CLND in the presence of multiple involved nodes or extracapsular extension of the tumor [26]. RT can be used to palliate symptoms in patients with metastatic disease. It contributes to cancer control by directly damaging the DNA of tumor cells and by immunomodulation [64, 65]. A retrospective study evaluating 26 patients with advanced MCC treated with radiation treatment as a single fraction of 8 Gy reported complete response (CR) in 47% of the tumors treated, as well as durable responses in the "in-field" treated lesions [63]. This treatment may improve the patient's quality of life compared to multiple RT sections. However, another analysis found much higher rates of durable local control with three fractions of 8 Gy [66]. Despite the specific regimen used, short-course radiation represents a valid palliative treatment option for metastatic MCC [65]. Moreover, short-course RT has been shown to be effective in patients with metastatic MCC who do not respond to immune checkpoint inhibitors [66].

Chemotherapy

Although cytotoxic chemotherapy has been commonly used to treat patients with advanced MCC, its role remains unclear in the literature; responses are rarely durable, and few studies have shown a survival benefit. The most common regimens recommended in the NCCN guidelines are carboplatin (or cisplatin) and etoposide or a combination of cyclophosphamide, doxorubicin (or epirubicin) and vincristine. MCC is very sensitive to chemotherapy [67–70], and initial response rates range from 53 to 76%; however, this high response rate is not durable, and tumors often recur within 4–15 months. A retrospective study of 6908 patients found that chemotherapy was not associated with an overall survival benefit in patients who presented with either local or nodal MCC [58]. Chemotherapy is also associated with a high risk of toxicity, particularly in patients aged > 65 years. Myelosuppression, sepsis, fatigue, alopecia, nausea and renal failure are the most common adverse events reported [67, 71]. Given the toxicity and lack of durable responses associated with chemotherapy, for each patient, the potential short-terms benefit should be compared to the potential risks [45, 72].

Emerging Therapies

Genetic and epigenetic alterations lead many cancers to produce antigens that may be recognized by the immune system. Immunotherapy is one of the most recent and expanding treatment modalities for metastatic MCC because (1) MCPyV-positive tumors express viral oncoproteins, and (2) MCPyV-negative tumors have a high mutational burden associated with neoantigen production. Both of these characteristics are used as key therapeutic targets in reactivating immune responses [72, 73]. However, no treatment directly targeting the tumor is available for use in combination with these checkpoint inhibitors (CPIs) to enhance their efficacy. We identified only one study in our literature search that characterized MCC line sensitivity to cellular lysis, with the authors identifying cell surface antigens that they used to carrying out direct targeting of this tumor

[74]. More studies to better define these new therapeutic targets are required.

Immune Checkpoint Inhibitors The programmed cell death receptor 1 (PD-1)/ programmed cell death ligand 1 (PD-L1) pathways contribute to local immune evasion by inhibiting T-cell response. PDL-1 is an immune checkpoint molecule that binds to its main receptor, PD-1, which is expressed by activated T lymphocytes. The complex PD-L1/PD-1 inhibits the signaling pathway involved in T-cell proliferation and cytotoxic activity, thereby preventing the stimulation of immune responses. Therefore, blocking the interaction between PD-L1 and PD-1 is a key therapeutic target in the reactivation of the immune response for the treatment of many tumors, including MCC [75]. PD-L1 is frequently expressed on MCC tumor cells and peritumoral immune cells while circulating MCPyV-specific T cells express PD-1. This characteristic makes these tumors excellent candidates for immunotherapy, and clinical trials evaluating checkpoint inhibitors therapy in metastatic MCC patients are ongoing [76–79].

Avelumab is a fully human PD-L1 inhibitor which blocks human immunoglobulin G1 (IgG1) lambda monoclonal antibody on the tumor cell, inhibiting the interaction between the PD-1 on T lymphocytes with the PD-L1 on the tumor cell, thereby preventing the inactivation of the T lymphocyte and keeping it available for tumor-cell destruction [75, 80]. Avelumab was approved in September 2017 by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a first-line treatment for patients (aged > 12 years) with metastatic MCC. These approvals were based on data from an open-label, single-arm, multicenter clinical trial [81, 82], in which 88 patients with metastatic MCC unresponsive to chemotherapy received at least one dose of avelumab (10 mg/kg body weight intravenously every 2 weeks). Patients were followed up for a median of 10.4 months, at which time 28 of the 88 patients (31.8%; 95.9% CI 21.9–43.1) had achieved an objective response, including 8 CR and 20 partial responses (PR). Avelumab also demonstrated a good safety profile [83]: no treatment-related grade 4 adverse events or treatment-related deaths were reported. Serious treatment-related adverse events were reported in five patients (6%), namely, enterocolitis, infusion-related reaction, increase in levels of aminotransferases, chondrocalcinosis, synovitis and interstitial nephritis; five grade 3 treatment-related adverse events occurred in four (5%) patients, namely, lymphopenia in two patients, blood creatine phosphokinase increase in one patient, aminotransferase increase in one patient, and blood cholesterol increase in one patient. This positive response was also reported in an human immunodeficiency virus (HIV)-positive patient treated with avelumab [82]. In December 2018, Kratzsch et al. described for the first time the occurrence of immune thrombocytopenia and anemia in a 77-year-old man treated with avelumab (10 mg/kg body weight every 2 weeks) for a metastatic MCC [84].

Pembrolizumab is a humanized IgG4 anti-PD-1 monoclonal antibody. It was the first immune CPI to demonstrate effective tumor regression in patients with metastatic MCC [85, 86]. Nghiem et al. conducted a multicenter phase 2 non-controlled study involving 26 with advanced MCC who had received no previous systemic therapy [73]. All patients received pembrolizumab at a dose of 2 mg/kg body weight every 3 weeks. The objective response rate among the 25 patients with at least one evaluation during treatment was 56% (95% CI 35–76); four patients had a CR and ten had a PR. With a median follow-up of 33 (range 7–53) weeks, relapses occurred in two of the 14 patients who had a response (14%). The response duration ranged from at least 2.2 months to at least 9.7 months. Pembrolizumab was effective in both MCPyV-positive and MCPyV-negative MCCs. It was well-tolerated; grade 3 or 4 adverse events occurred only in 15% of the patients [73]. Based on this result pembrolizumab was added to the 2017 NCCN treatment options for metastatic MCC. In another study, Winkler et al. reported the case of a 80-year-old patient with metastatic MCC who was successfully treated with the reintroduction of pembrolizumab after disease progression during a 4-month period without therapy [87].

Nivolumab is another fully human IgG4 anti-PD-1 antibody with clinical activity in advanced MCC still under investigation [88]. A phase 1/2 trial (CheckMate358) is currently investigating the safety and effectiveness of nivolumab and nivolumab combination therapy in virus-associated tumors, including MCC. Two earlier cases of a good response have been reported. In 2016, Walocko et al. described the case of an 80-year-old man with advanced MCC who achieved a significant and durable response to nivolumab (3 mg/kg body weight intravenously every 2 weeks for 6 cycles) [89, 90]. In 2015, Mantripragada and Birnbaum reported the case of a young patient with advanced MCC who obtained an impressive response to nivolumab [86].

Several immunotherapies that act through mechanisms other than inhibition of PD-1 and PDL-1 are currently under investigation for the treatment of metastatic MCC. Therapeutic combinations that include the CTLA-4 antibody ipilimumab [91] are currently being studied. A phase II randomized trial investigating ipilimumab as adjuvant therapy after excision versus observation is currently underway [92]. In 2017, a case series of five patients with metastatic MCC treated with ipilimumab (3 mg/kg body weight every 3 weeks) reported controversial results for ipilimumab in advanced MCC. Previous to that case series, only one report on a patient who achieved a reduction in cutaneous MCC lesions during combined therapy of ipilimumab and chemotherapy had been described [93]. Autoimmune toxicity, which most commonly affects the skin, gastrointestinal tract, liver and endocrine system represents the most frequent side effects of immunotherapy and is the consequence of T-cell activation against the host tissue. Colitis, myositis, hypothyroidism and autoimmune insulin-dependent diabetes mellitus are the most frequently described immune-related adverse events in patients with MCC treated with immunotherapeutics agents. Therefore, patients with autoimmune disorders, HIV infection and hematologic or solid malignancies are commonly excluded from participating in clinical trials except for clinical case reports and small cohort studies [94, 95]. Furthermore, resistance to this therapy is frequent due to the activation of adaptive resistance, with upregulation of alternative immune checkpoints. An interesting strategy for treating patients advanced MCC not responding to the classic immune CPIs is the use of other immunotherapies, such as intratumoral interferon, interleukin-12 DNA electroporation and Toll-like receptor 4 agonists; these therapies are still under investigation [96–98].

The main trials which have investigated immune CPIs are shown in Table 1.

Targeted Molecular Therapy While immunotherapy has demonstrated a high response rate in immunocompetent patients (> 50% in chemotherapy-naive patients) and the overall survival is durable, alternatives to immunotherapy are needed for patients with advanced-stage MCC who are immunosuppressed, transplanted patients who are at risk of transplant rejection and patients who do not respond to classic immunotherapy [45, 72]. Several types of targeted therapies have been investigated in MCC cell lines and xenograft models, and ongoing prospective clinical trials are studying these agents [99, 100]. An interesting strategy for advanced MCC not responding to immune CPIs is the use of natural killer cell-based treatment. An ever-increasing body of evidence supports the importance of angiogenesis in the pathogenesis of MCC tumors that express vascular endothelial growth factors (VEGF), such as VEGF-A, VEGF–C, VEGF-R2, platelet-derived growth factor (PDGF)-b and C-kit [13].

Pazopanib and cabozantinib are inhibitors of multiple receptor tyrosine kinases (VEGFR-1, -2 and 3 and C-kit). Pazopanib also inhibits PDGF-α and -β. To date, little data have been reported in the literature on the utility of pazopanib and cabozantinib in MCC [101]. Tarabadkar et al. described a case series in which the VEGFR tyrosine kinase inhibitors (TKIs) pazopanib and cabozantinib were used successfully in five patients with metastatic MCC who had previously been treated with cytotoxic therapy [102]. Prior to this case series, only a single case of metastatic MCC successfully treated with pazopanib had been described [103]. Prospective clinical trials investigating either pazopanib and

Table 1 Main trials investigating immune checkpoint inhibitors

Drug	Authors	Number of cases	Dosage	Objective response
Avelumab (PD-L1 inhibitor)	Kaufman et al. [80, 81]	88	10 mg/kg intravenously every 2 weeks	28 (31.8%): 8 CR 20 PR
Pembrolizumab (PD-1 inhibitor)	Nghiem et al. [73]	26	2 mg/kg intravenously every 3 weeks	14 patients (56%): 4 CR 10 PR
Nivolumab (PD-1 inhibitor)	Topalian et al. [88]	25	240 mg every 2 weeks	64% objective response
Ipilimumab (anti CTLA-4)	Schadendorf et al. [92] (ongoing)	–	3 mg/kg every 3 weeks	–

CTLA-4 Cytotoxic T-lymphocyte–associated antigen 4, *CR* complete response, *PD-1* programmed cell death receptor 1, *PD-L1* programmed cell death ligand 1 *PR* partial response

cabozantinib are undergoing [104]. To date, activating tyrosine-kinase mutations have not been detected in MCCs; consequently, there is little evidence that tyrosine kinase inhibition is an effective treatment approach for patients with MCC [105]. Complete remission following treatment with imatinib, a targeted inhibitor of some tyrosine kinase receptors, including the C-kit receptor, was reported in a patient with an inoperable MCC of the eyebrow [106], although a phase II clinical trial evaluating the efficacy of imatinib in advanced MCC was prematurely discontinued because there was no evidence of clinical efficacy [105].

Mutations which activate phosphatidylinositol 3-kinase–mammalian target of rapamycin (PI3K–mTOR) have been found in some MCPyV-negative patients, although this specific type of mutation is very rare [106, 107]. There has only been a single reported case of a patient with advanced MCC carrying a known PI3K mutation who was successfully treated with idelalisib, a PI3K inhibitor, resulting in a rapid and complete remission [108]. Several prospective studies are currently investigating the safety and efficacy of mTOR inhibition in patients with advanced MCC.

MCC is a neuroendocrine cancer that expresses somatostatin receptors (SSTs), in particular SST-2. Therefore, somatostatin analogs are being investigated for both molecular imaging and the treatment of advanced MCC [109]; however, data are currently lacking. Response following treatment with lanreotide, a somatostatin analog has been reported in only one case of MCC [110], and a phase II trial evaluating its efficacy and safety is ongoing [111]. In a prospective study involving 58 patients with neuroendocrine tumors treated with octreotide, another somatostatin analog, a PR rate of only 3% was reported [112].

The cases of advanced MCC successfully treated with new targeted molecular therapies are shown in Table 2.

As, poly-ADP ribose polymerase 1 (PARP1) is overexpressed in advanced MCC, as in small lung cell cancer. Trials on the efficacy of PARP inhibitors are ongoing with the aim to explore other novel therapeutic options for inoperable MCC [113].

Table 2 Cases of advanced Merkel cell carcinoma successfully treated with new targeted molecular therapies

Drug	Authors	Number of cases	Dosage	Objective response
Pazopanib (anti-VEGFR-1,2,3 and C-kit	Tarabadkar et al. [102]	4	800 mg daily	1 CR 3 PR
Cabozantinib (anti- VEGFR-1,2,3 and C-kit)	Tarabadkar et al. [102]	1	60 mg daily	PR
Imatinib (tyrosine kinase inhibitor)	Loader et al. [106]	1	400 mg daily	CR
Idelalisib (PI3K-inhibitor)	Shiver et al. [108]	1	150 mg twice daily	CR
Lanreotide (somatostatin analog)	Fakiha et al. [110]	1	15 mg i.m. injection every two weeks	CR

PI3K Phosphoinositide 3-kinase, *VEGFR* vascular endothelial growth factor

DISCUSSION

Merkel cell carcinoma is a rare and aggressive skin cancer with a neuroendocrine phenotype. Incidence varies according to geographic region, but is increasing worldwide, with higher incidence rates among older males and subjects with light skin [1, 3]. Infection with MCPyV, ultraviolet radiation exposure and immunosuppression are the main factors associated with the pathogenesis of MCC. Most frequently, MCC presents as local disease, but up to 30% of cases may involve regional lymph node and distant metastases. Surgery is the first-line treatment for localized disease, followed by adjuvant radiation or chemoradiation [9]. In the advanced form of MCC, chemotherapy is considered to be the standard treatment, despite the high rate of adverse events associated with the chemotherapeutic regimens. In addition, the majority of regimens used are associated with toxicity and worsening of the immunosuppression status. The therapeutic landscape for metastatic MCC is evolving rapidly [28, 114], and recent advances in the development of well-tolerated immunotherapy agents [30, 115] have the potential to provide effective treatment options for patients with advanced MCC. Immune checkpoint blockade is an exciting treatment option for patients with metastatic MCCs. Avelumab (anti-PD-L1) and pembrolizumab (anti-PD-1) have shown promising results in clinical trials performed on patients with advanced MCC. In this context, given its therapeutic response and safety profile, avelumab was approved in September 2017 by the US FDA and EMA as a first-line treatment for patients (aged > 12 years) with metastatic MCC [80]. Despite these successes several immune-related adverse events during treatment with immune CPIs have been reported, and approximately 50% of patients with metastatic MCC do not respond or experience disease progression after their initial response to treatment with CPIs, underscoring the need for novel strategies to broaden antitumor immune responses in these patients [94, 95, 116]. A growing body of literature suggests an increased rate of response in patients with metastatic MCC treated with short-course RT combined with immune CPIs [117]. There is also increasing evidence supporting the importance of angiogenesis in the pathogenesis of MCC tumors that express VEGFs, such as VEGF-A, VEGF–C, VEGF-R2, PDGF-b, and C-kit [13]. Several therapeutic agents acting on these factors have been studied, and trials evaluating their efficacy are ongoing. According to the NCCN Clinical Practice guidelines, continuous follow-up for patients with diagnosed MCC is recommended. A complete physical exam, including lymph node evaluation, is required

every 3–6 months for the first 3 years after diagnosis and every 6–12 months thereafter. The follow-up should also include the screening of adverse events related to treatment with immune CPIs. Contrast-enhanced brain magnetic resonance imaging and contrast-enhanced neck/chest/abdomen/pelvis computed tomography are also recommended to identify and quantify regional and distant metastases [118].

CONCLUSIONS

Evidence on the efficacy and safety of immunotherapy and targeted molecular therapy is still limited, and long-term data are lacking [13, 28]. Consequently, physicians usually have to rely on experiences reported in case reports and case series. Hence, in everyday practice clinicians must follow a general approach maximizing the benefit–risk ratio. More prospective, multicenter studies are needed to evaluate further treatment options to develop international guidelines on metastatic MCC treatment.

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