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REVIEW – CLINICAL ONCOLOGY

Immune checkpoint blockade for Merkel cell carcinoma: actual findings and unanswered questions

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Abstract

Purpose Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma arising from the skin. We aimed to review and deal with some of the most relevant controversial topics on the correct use of immunotherapy for the treatment of MCC.

Methods The primary search was carried out via PubMed, EMBASE, and the Cochrane Library (until 31st May, 2018), while other articles and guidelines were retrieved from related papers or those referenced in these papers. Additionally, we performed an extensive search on ClinicalTrials.gov to gather information on the ongoing clinical trials related to this specific topic.

Results We performed an up-to-date critical review taking into account the results of both retrospective and prospective published studies evaluating these issues: Are there any predictive criteria of response to immunotherapy? What is the correct place of immunotherapy in the treatment algorithm of MCC? What is the best choice after immunotherapy failure? What to do with patients for whom immunotherapy is not been feasible or contraindicated? How long should immunotherapy be prolonged, and what follow-up should be offered after complete response?

Conclusion The therapeutic landscape of MCC is rapidly evolving: many open issues will probably be resolved, and many other questions are likely to arise in the next few years. The results of ongoing prospective clinical trials and of several other studies on these issues are eagerly awaited.

Keywords Merkel cell carcinoma · Neuroendocrine tumours · Immune checkpoint inhibitors · Avelumab · Pembrolizumab · Therapy

Introduction

Merkel cell carcinoma (MCC) is an uncommon, aggressive neuroendocrine carcinoma arising in the dermoepidermal junction of the skin, that was originally described less than 50 years ago (Toker 1972). MCC, which is the second most common cause of skin cancer death after melanoma, has been traditionally believed to arise from skin mechanoreceptors with touch-sensitivity function (Merkel cells, as named after the German scientist who discovered them in 1875), but its histogenesis is still controversial. According to another hypothesis, MCC could originate from an immature totipotential stem cell with neuroendocrine features acquired during malignant transformation (Tilling and Moll 2012).

The estimated annual incidence of MCC in 2006 was 0.6 per 100,000 person (Albores-Saavedra et al. 2010), with higher incidence rates among older males and subjects with

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light skin. However, a younger age and higher incidences are observed in immunocompromised people, such as organ transplant recipients, HIV-infected subjects, people using immunosuppressant medications, and those with lymphoproliferative disorders or other malignancies (Tadmor et al. 2011; Engels et al. 2002; Clarke et al. 2015). The main factors associated with the pathogenesis of MCC include infection with the Merkel cell polyomavirus (MCPyV), ultraviolet radiation exposure (UVB irradiation), and immunosuppression. The incidence of MCC is increasing more rapidly than other skin tumours, such as malignant melanoma, probably due to longevity, improved detection, and increased reporting (Hodgson 2005; Prewett and Ajithkumar 2015).

Most frequently, MCC presents with local disease, but regional lymph node and distant metastases may be present in up to 30% of new cases. In a minority of cases, MCC is diagnosed as a lymph node metastasis without an identifiable primary lesion, which may have spontaneously regressed or be occult (Deneve et al. 2012). Typically, patients with occult primary MCCs have higher tumour mutational burden, lower association with MCPyV, and better prognosis than those with known primary, possibly due to an effective immune response and immunologically mediated regression (Uchi 2018).

Even though several clinicopathologic features may have an influence on prognosis (e.g. increasing age, male sex, histological features, MCPyV serology, and immune status), the involvement of regional lymph nodes or distant metastases at presentation are the most important predictors of survival for MCC. In 2017, a new MCC-specific consensus staging system has been developed by the American Joint Committee on Cancer (AJCC), taking into account size of the primary lesion and presence of tumour invasion (T), presence of nodal metastasis (N), and distant metastasis (M) (Bichakjian et al. 2017). Based upon TNM information, patients with MCC are assigned to prognostic stage groups: stages I and II MCC include patients with local disease only (≤ 2 and > 2 cm maximum tumour dimension, respectively), stage III includes patients with regional nodal disease, and stage IV is for patients with metastases beyond the regional lymph nodes.

The treatment depends on the stage of the disease, the tumour site and any comorbid conditions. Excision of MCC with 1- to 2-cm negative margins (with sentinel lymph node biopsy for patients with clinically negative nodes) is the mainstay of therapy for local disease (stage I and II), followed by adjuvant radiotherapy. The latter can be omitted with small tumours (≤ 1 cm), wide excision margins (> 2 cm), negative lymph nodes, and no other adverse features (such as immunosuppression).

Positive nodal disease (stage III), affecting one-third of patients, should be treated with neck dissection and adjuvant radiotherapy. Radiotherapy (45–50 Gy for microscopic disease and 50–60 Gy for macroscopic disease) is an option for primary therapy in patients who cannot undergo or not amenable to surgical interventions.

Until recently, guidelines suggested chemotherapy in cases of metastatic, advanced-stage MCC (stage IV), however, recommending enrolment in clinical trials due to the poor long-term outcomes of chemotherapy. Systemic chemotherapy with therapeutic regimes derived from small-cell lung cancer due to the similar neuroendocrine properties to MCC, and has been typically performed with platinum, etoposide, doxorubicin, cyclophosphamide, vincristine, paclitaxel, and topotecan, alone or in combinations. Albeit high response rates (from 52 to 61%), response duration is usually short (3–15 months) and survival benefits questionable (Prewett and Ajithkumar 2015; Hasan et al. 2013). The few real-world, retrospective studies which assessed second-line or later chemotherapy showed low objective response rates (ORRs; from 8.8 to 23.0% with no complete responses) and very limited durability (1.3–3.3 months) (Iyer et al. 2016; Becker et al. 2017). Furthermore, most regimens are associated with considerable toxicity and can worse immunosuppression, paradoxically stimulating the tumour (Nghiem et al. 2017; Rabinowitz 2017). Indeed, considerable evidence suggests that immunosuppression contributes significantly to the course and prognosis of MCC, implying that therapeutic agents that promote antitumour immune responses might be beneficial in MCC.

One mechanism contributing to tumour proliferation is the expression of programmed cell death ligand 1 (PD-L1, an immune-inhibitory ligand) in the tumour microenvironment. PD-L1 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 signalling pathways involved in T-cell proliferation, survival and cytotoxic activity (including cytokine and enzymes release), preventing overstimulation of immune responses. Tumour associated inflammation has been shown to upregulate PD-L1 expression, thus enabling tumours to avoid and escape immune surveillance. Therefore, blocking the interaction between PD-1 and PD-L1 is a key therapeutic target in the reactivation of the immune response and a promising target for many tumours, including MCC. Indeed, PD-L1 expression has also been described in MCC cells and in tumour-infiltrating and peritumoural leukocytes, providing a rationale for treatment with immune checkpoint inhibitors (ICIs) in MCC (Nghiem et al. 2017). Both avelumab (MSB0010718C; anti-PD-L1) and pembrolizumab (anti-PD-1) have recently shown promising results in clinical trials performed on patients with metastatic MCC, as discussed further in the manuscript. Results of these trials led to the addition of ICIs in the most recent update of the National Comprehensive Cancer Network (NCCN) Clinical Practice guidelines as a treatment option

for stages III–IV MCC (Bichakjian et al. 2018). Since 2017, based on its therapeutic responses and safety profile, avelumab has been approved in the USA, the European Union, Switzerland, and Japan for the treatment of metastatic MCC, in first and second-line settings. Furthermore, on December 2018, the US Food and Drug Administration granted accelerated approval to pembrolizumab for adult and paediatric patients with recurrent locally advanced or metastatic MCC. Most likely, chemotherapy will no longer represent the first option for advanced stage MCC.

Recent prospective clinical trials in patients with advanced MCC revolutionised medical therapy of stage IV MCC, showing the durable efficacy and favourable tolerability of anti–PD-1 or anti–PD-L1 ICIs in the first-line or second-line and later settings.

However, many critical issues on the correct use of ICIs for the treatment of MCC still remain and many questions are still unanswered (Table 1).

With the aim to review and deal with some of the most relevant controversial topics on the management of MCC with ICIs, we performed an up-to-date critical review taking into account the results of both retrospective and prospective published studies. The primary search was carried out via PubMed, EMBASE, and the Cochrane Library (until 31st May, 2018), while other articles and guidelines were retrieved from related papers or those referenced in these papers. The search was restricted to reports published in English. Additionally, we performed an extensive search on ClinicalTrials.gov to gather information on the ongoing clinical trials related to this specific topic.

Are there any predictive criteria of response to immunotherapy?

Viral antigens of virus-positive MCC can act as excellent immune targets. On the other hand, virus-negative MCC express a higher load of somatic mutations and putative tumour neoantigens, probably induced by UV irradiation (Goh et al. 2016; Amaral et al. 2017). Therefore, both virus-positive and virus-negative MCC express non-self antigens making these tumours excellent candidates for immunotherapy (Goh et al. 2016; Amaral et al. 2017; Baker et al. 2018). However, since checkpoint-based immunotherapy is not effective for all MCC patients, it would be of the uttermost importance to better understand the cellular and genomic determinants of the immune response in this setting, to better select candidate patients for immunotherapy.

Indeed, durable responses to therapies involving the PD-1/PD-L1 axis have recently been shown to occur irrespectively of tumour MCPyV status, as well as both in patients with PD-L1 + and with PD-L1- tumours (Kaufman et al. 2016; Nghiem et al. 2016). This may be due to the relative small number of patients treated in the two phase II studies performed with avelumab and pembrolizumab. As an example, PD-L1 expression in the primary tumour and/or in the metastatic lesions is heterogeneous, thus a negative single biopsy may not be representative of all the tumours (Becker et al. 2018).

Other characteristics of the tumour microenvironment could also modulate the immune response correlating with clinical outcomes of anti-PD-1 or anti-PD-L1 therapy, such as the presence of CD8 + T-cell infiltrates, the expression

Table 1 Controversial issues about immunotherapy for MCC

Are there any predictive criteria of response to immunotherapy? (i.e. can patients be selected for a better response to immunotherapy?)
What is the place of immunotherapy in the treatment algorithm of Merkel cell carcinoma?
Can immunotherapy be helpful as first-line therapy for stage IV disease, or it should be used only after PD with systemic chemotherapy?
Can immunotherapy be an option as an adjuvant treatment for regional disease (stage III MCC)?
Is there a role for neoadjuvant therapy with immune checkpoint inhibitors?
What are the advantages and the potential drawbacks of the association of immunotherapy and radiotherapy?
What are the options for patients who progress after immunotherapy?
Patients who not respond to immunotherapy
Patients who develop resistance or escape to immunotherapy
What are the options for patients who are not candidates for immunotherapy?
Patient categories who were excluded from clinical trials
Patients with active autoimmune disorders
Patients who underwent organ or bone marrow transplantation
Patients with abnormal organ and bone marrow function
Patients with immunodeficiency (e.g. HIV) or ongoing systematic immunosuppressive therapy
How long should treatment with immune checkpoint inhibitors be prolonged after complete response?
What follow-up should be performed after complete response?

of additional immune checkpoints, and the gene-expression profile (Schadendorf et al. 2017; Becker et al. 2018).

Ongoing research in MCC is trying to identify reliable biomarkers that will help predict which patients have more chances to respond to immunotherapy. Implementing immunotherapy for MCC might require, in the future, precision medicine approaches for any given case (Cassler et al. 2016). Actually, however, no powerful predictor of response can be used to decide whether to use immunotherapy in a patient with MCC (Hauschild and Schadendorf 2016; Bommareddy and Kaufman 2017).

As of today, immunotherapy should be considered for first-line treatment in patients with advanced MCC, since a trend toward a higher response rate has been observed in patients with fewer lines of prior treatment (D'Angelo et al. 2018). Furthermore, previous chemotherapy has recently shown to decrease the expression of both PD-L1 and PD-1 in different settings (Rojkó et al. 2018).

What place for immunotherapy in the treatment algorithm of Merkel cell carcinoma?

Immunotherapy is currently recommended for patients with disseminated disease or recurrence. Data from prospective clinical trials showed that the rates of durable responses are improved with immunotherapy than cytotoxic treatment, with minor side effects both in the first and second/later line of therapy (Kaufman et al. 2016; Nghiem et al. 2016) and a better cost-effectiveness (Bharmal et al. unpublished results).

In a multicenter Phase II trial of 88 patients with stage IV chemotherapy refractory MCC, treatment with avelumab showed durable responses: the ORR was 33% (95% CI 23–44), with 74% of responses lasting ≥ 1 year and a 1-year overall survival (OS) rate of 52% (95% CI 41–62) in second-line and further-line therapies (Kaufman et al. 2016, 2018). In addition, a trend towards a higher response rate was observed in those patients with fewer lines of previous chemotherapy. Preliminary data have been recently published on the favourable effects of avelumab in treatment naïve patients with metastatic MCC, showing an ORR of 62.1% and a CR of 13.8% at 6 months (D'Angelo et al. 2018). Interestingly, a cross-study analysis of avelumab after ≥ 1 line of chemotherapy in metastatic MCC after ≥ 1 year of follow-up was performed, finding that second-line chemotherapy was associated with a lower ORR than avelumab (9–23% vs. 33%, respectively), and with a 1-year progression-free survival (PFS) rate of 0% vs. 30%, respectively (Kaufman et al. 2018). Data from a large cohort of patients, enrolled in a global expanded access program and treated with avelumab as second-line treatment in a real world setting, showed an ORR (as evaluated by the treating physician) of 52.5% in the global population and 54.8% in the European population (Nathan et al. unpublished results).

In another multicenter, phase II non-controlled study in patients with advanced (stage III or IV) MCC, pembrolizumab administered as a first-line treatment showed an ORR of 56% (95% CI 35–76), with 86% of responses ongoing at data cutoff (Nghiem et al. 2016). Interestingly, in the expanded phase of this study ORR was 50% (95% CI 34.2–65.8; CR 19%, PR 31%) in 42 patients with ≥ 21 week of follow-up. OS rate at 18 months was 68% and median OS was not reached. Among 21 confirmed responders, median response duration was not reached (range 3.9–25.6 months) (Nghiem et al. 2018).

Other immunotherapies being investigated in MCC include ipilimumab and nivolumab (anti-PD-1) as first- or second-line treatment of unresectable local and/or metastatic MCC (stages II–IV) (Topalian et al. 2018). As an example, preliminary results on nivolumab as first- or second-line treatment, in patients with advanced MCC, showed an ORR of 68% and a PFS at 3 months of 82% (ongoing trial NCT02488759).

Collectively, these data suggest that immunotherapies can substantially improve the outcome of patients with metastatic MCC. Therefore, avelumab, nivolumab and pembrolizumab are currently recommended for patients with advanced MCC.

Immunotherapy as an adjuvant treatment for regional disease (stage III)

The possibility to use immunotherapy in the adjuvant setting following surgical resection of local MCC seems appropriate, due to the consideration that an early treatment of a tumour correlates with an improved prognosis and to the successful approach in other tumours such as melanoma (Eggermont et al. 2015, 2018; Gibney et al. 2015; Weber et al. 2017).

Currently, the efficacy of avelumab as adjuvant therapy versus placebo in patients with stage III/IIIb MCC, with or without radiotherapy, is under investigation (NCT03271372). A clinical trial on nivolumab and ipilimumab in the adjuvant setting (NCT02196961) is partially ongoing, too (ADMEC-O) (See Table 2). In the arm of this study evaluating ipilimumab in 40 patients within 12 weeks after complete tumour resection, no significant differences were observed between ipilimumab and observation (hazard ratio 1.8; 95% CI 0.3–10; $p = 0.48$) (Becker et al. unpublished results). However, patients in the treatment arm had a significantly increased incidence of adverse events. For these reasons, the enrolment in this arm was stopped.

Therefore, the use of PD-1/PD-L1 inhibitors in the adjuvant setting has been a major discussion topic in the last

Table 2 Ongoing active clinical trials for MCC. (source: https://www.clinicaltrials.gov)

NCT	Title	Phase	Intervention
NCT02196961	Adjuvant Therapy of Completely Resected Merkel Cell Carcinoma With Immune Checkpoint Blocking Antibodies versus Observation (ADMEC-O)	II	Ipilimumab Nivolumab
NCT02488759	Non-Comparative, Open-Label, Multiple Cohort, Phase 1/2 Study of Nivolumab Monotherapy and Nivolumab Combination Therapy in Subjects With Virus-Positive and Virus-Negative Solid Tumors	I II	Nivolumab Ipilimumab BMS-986016 Daratumumab
NCT03167164	NANT Merkel Cell Carcinoma (MCC) Vaccine: Combination Immunotherapy in Subjects With MCC Who Have Progressed on or After Anti-programmed Death-ligand 1 (PD-L1) Therapy	I II	Avelumab Bevacizumab Capecitabine Cisplatin Cyclophosphamide 5-fluorouracil Leucovorin Nab-Paclitaxel Omega-3-acid ethyl esters Stereotactic Body Radiation Therapy +5 biological
NCT02465957	Phase II Study of aNK (Activated NK-92 Natural Killer Cells) Infusions in Combination With ALT-803 (IL-15) in Patients With Stage III (IIIB) or Stage IV Merkel Cell Carcinoma (MCC)	II	aNK (NK-92)
NCT02036476	Cabozantinib in Recurrent/Metastatic Merkel Cell Carcinoma	II	Cabozantinib
NCT03071406	A Phase II, Randomized, Multi-institutional Study of Nivolumab and Ipilimumab versus Nivolumab, Ipilimumab and Stereotactic Body Radiation Therapy for Metastatic Merkel Cell Carcinoma	II	Nivolumab Ipilimumab Stereotactic Body Radiation Therapy
NCT03271372	A Multicenter, Randomized, Double-Blinded, Placebo-Controlled, Phase III Trial of Adjuvant Avelumab (Anti-PDL-1 Antibody) in Merkel Cell Carcinoma Patients With Clinically Detected Lymph Node Metastases	III	Avelumab Placebo
NCT02155647	A Phase II, Open-Label, Multicenter Trial to Investigate the Clinical Activity and Safety of Avelumab (MSB0010718C) in Subjects With Merkel Cell Carcinoma	II	Avelumab
NCT01013779	A Phase II Efficacy Study of Chemo-Radiotherapy in PET Stage II and III Merkel Cell Carcinoma of the Skin	II	Carboplatin Etoposide Radiotherapy
NCT02584829	Study to Evaluate Cellular Adoptive Immunotherapy Using Polyclonal Autologous CD8 + Antigen-Specific T Cells for Metastatic Merkel Cell Carcinoma in Combination With MHC Class I Up-Regulation and the Anti-PD-L1 Antibody Avelumab	I II	Avelumab MCPyV TAg-specific Polyclonal Autologous CD8-positive T Cells Radiation Therapy Recombinant Interferon Beta
NCT02819843	A Phase II Randomized Trial of Intralesional Talimogene Laherparepvec (TALIMOGENE LAHERPAREPVEC) With or Without Radiotherapy for Cutaneous Melanoma, Merkel Cell Carcinoma, or Other Solid Tumors	II	TALIMOGENE LAHERPAREPVEC (TVEC) Hypofractionated Radiotherapy
NCT03304639	A Randomized Phase II Study of Anti-PD1 Antibody [MK-3475 (Pembrolizumab)] Alone versus Anti-PD1 Antibody Plus Stereotactic Body Radiation Therapy in Advanced Merkel Cell Carcinoma	II	Pembrolizumab Stereotactic Body Radiation Therapy
NCT02267603	A Phase II Study of MK-3475 in Patients With Advanced Merkel Cell Carcinoma (MCC)	II	Pembrolizumab
NCT02978625	A Phase II Study of Talimogene Laherparepvec Followed by Talimogene Laherparepvec + Nivolumab in Refractory T Cell and NK Cell Lymphomas, Cutaneous Squamous Cell Carcinoma, Merkel Cell Carcinoma, and Other Rare Skin Tumors	II	Nivolumab Talimogene Laherparepvec

Table 2 (continued)

NCT	Title	Phase	Intervention
NCT03458117	A Phase I, Open Label, Single Arm, Single Centre Study to Evaluate Mechanism of Action of Talimogene Laherparepvec (T-VEC) in Locally Advanced Non-melanoma Skin Cancer	I	Talimogene Laherparepvec (T-VEC)
NCT03435640	A Phase 1/2, Open-label, Multicenter, Dose Escalation and Dose Expansion Study of NKTR-262 in Combination With NKTR-214 and in Combination With NKTR-214 Plus Nivolumab in Patients With Locally Advanced or Metastatic Solid Tumor Malignancies	I II	NKTR-262 NKTR-214 Nivolumab
NCT02890368	A Phase 1 Dose Escalation Trial of Intratumoral Injections of TTI-621 in Subjects With Relapsed and Refractory Percutaneously-Accessible Solid Tumors and Mycosis Fungoides	I	TTI-621 TTI-621 + PD-1/PD-L1 inhibitor TTI-621 + pegylated interferon-α2a TTI-621 + T-Vec TTI-621 + radiation
NCT02643303	A Phase 1/2 Study of In Situ Vaccination With Tremelimumab and IV Durvalumab (MEDI4736) Plus the Toll-like Receptor Agonist PolyICLC in Subjects With Advanced, Measurable, Biopsy-accessible Cancers	I II	Durvalumab Tremelimumab Poly ICLC
NCT03212404	A Phase 1, Open-label, Multicenter, Dose-escalation Study of CK-301 Administered Intravenously as a Single Agent to Subjects With Advanced Cancers	I	CK-301
NCT03241173	A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of INCAGN01949 in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies	I II	INCAGN01949 Nivolumab Ipilimumab
NCT03071757	A Multicenter, Phase 1, Open-Label, Dose-Escalation Study of the Safety, Tolerability and Pharmacokinetics of ABBV-368 as a Single Agent and Combination in Subjects With Locally Advanced or Metastatic Solid Tumors	I	ABBV-368 Nivolumab
NCT03000257	A Multicenter, Phase 1, Open-Label, Dose-Escalation Study of ABBV-181, a Monoclonal Antibody, as Monotherapy and in Combination With Another Anti-Cancer Therapy in Subjects With Advanced Solid Tumors	I	Rovalpituzumab Tesirine ABBV-181

years. Some of the challenges of assessing these drugs in the adjuvant setting include the identification of which patients may have the best benefit from it, without exposing to unnecessary, ineffective, and toxic treatment (Napolitano et al. 2018).

Immunotherapy as a neoadjuvant therapy

The use of ICIs as a neoadjuvant treatment, before surgical resection, has been investigated, resulting advantageous in mice models and in humans with non-small-cell lung carcinoma (NSCLC). The mechanism of action seems to be the generation of circulating T cells, which may improve protection against tumour growth (Liu et al. 2016; Forde et al. 2018). Neoadjuvant ipilimumab treatment showed favourable effects in patients with regionally advanced melanoma (Tarhini et al. 2014). Currently, a study evaluating the combination of neoadjuvant ipilimumab and nivolumab in patients with melanoma is ongoing (NCT02977052), while no data are available for patients with MCC.

Immunotherapy ± radiotherapy

The combination of immunotherapy and radiotherapy has been shown to exert favourable effects on tumour control, due to a synergistic effect (Sharabi et al. 2015).

Indeed, radiotherapy has been demonstrated to stimulate T-cell activation and proliferation by releasing tumour antigens, and to modulate the expression of immune checkpoint ligands, including PD-L1, on tumour cells (Parker et al. 2013; Deng et al. 2014). In addition, it is correlated to an abscopal effect, a phenomenon in which tumour regression occurs in non-irradiated lesions (Demaria et al. 2004). For these reasons, sequential use of radiotherapy and ICI may be associated with an improvement of relapse free survival.

Available data on NSCLC and metastatic melanoma have shown clinical benefit when immunotherapy was

given after radiotherapy (Shaverdian et al. 2017; Grimaldi et al. 2014). Currently, the combination of pembrolizumab with or without stereotactic body radiation therapy (SBRT), and the combination of nivolumab and ipilimumab with or without SBRT, in advanced MCC, are under investigation (NCT03304639 and NCT03071406) (See Table 2).

What after immunotherapy?

Patients not responding to immunotherapy

For those patients who do not respond to immunotherapy, other approaches are being explored for MCC.

The intratumoural immune infiltration of pro- and anti-inflammatory molecules stimulating the immune system has been evaluated. Glucopyranosyl lipid-A stable emulsion (GLA-SE), a Toll-like receptor 4, was reported to be associated with a CR in one patient and a quite long recurrence free period in patients with stage IIIB MCC, together with a partial response (PR) in 2 out of 7 patients with stage IV MCC (Bhatia et al. 2016). Other cytokines such as IL-2 and TNF-α were also injected in the MCC lesion with a 30% of CR and 10% of PR, while 40% of patients showed stable disease (SD) (Bhatia et al. 2016). The use of TTI-621, a recombinant fusion protein targeting CD 47 (NCT02890368) is being tested in an early phase trial.

An interesting strategy for advanced MCC not responding to ICI is the use of a Natural Killer (NK) cells based therapy, which preliminarily provided a CR in one patient (NCT02465957). The infusion of T cells plus HLA upregulation was also evaluated without benefits when administered alone, while three CR were observed when added in combination with avelumab (Chapuis et al. 2014; Paulson et al. 2017). Other clinical trials on T cell regulation therapy are under investigation (NCT03241173 and NCT03071757).

Another strategy is based on the use of mutated viral genes, which active proliferative pathways in tumour cells allowing the virus to replicate and kill these cells (Andtbacka et al. 2015). Other agents with similar activity are being explored such as the intralesional talimogene laherparepvec, a recombinant herpes simplex type-1 virus-based agent (NCT02819843, NCT03458117 and NCT02978625).

Further treatment strategies include targeted therapies, inhibiting molecules required for tumour growth and progression. Some of them are based on tropomyosin receptor kinase A expression or AKT/PI3K pathway, mTOR complexes, tyrosine kinases, such as VEGF and PDGF receptors, or survivin protein (Shiver et al. 2015; Davids et al. 2009; Samlowski et al. 2010; Wehkamp et al. 2017; Iwasaki et al. 2015; Arora et al. 2012; Brunner et al. 2008). Recently, the use of cabozantinib in patients with advanced, progressive MCC after platinum-based chemotherapy did not demonstrate any benefit in terms of disease control (Rabinowits et al. 2018). However, a recent case series of five patients treated with pazopanib or cabozantinib showed a clinical benefit with a stabilization of disease (Tarabadkar et al. 2018). In addition, preliminary results from a clinical trial investigating pazopanib showed a PR rate of 19% and a disease control rate (OR + SD for > 12 weeks) of 56% (clinicaltrialsregister.eu; Eudra CT# 2011-003226-27) (Nathan et al. 2016). Currently, clinical trials on cabozantinib for MCC are ongoing (NCT02036476).

The overexpression of somatostatin receptor 2 has been reported in patients with MCC (Guitera-Rovel et al. 2001) representing a potential target for both imaging and treatment (Buder et al. 2014; Meier et al. 2004). However, results from studies evaluating the efficacy of somatostatin analogues in MCC are not available, yet (NCT 02351128) (See Table 2).

Other immune checkpoint inhibitors

The use of antibodies blocking the CTLA4 expression (ipilimumab) in T cells can be considered for those patients where PD-1 pathway blockade is ineffective, trying to improve the immune response. Clinical trials investigating ipilimumab efficacy in MCC are ongoing (NCT02488759, NCT02196961 and NCT03071406).

Further, atezolizumab, durvalumab, tremelimumab and daratumumab, human IgG1 anti-PD-L1 monoclonal antibodies, are currently under investigation for the treatment of advanced MCC (NCT02471846, NCT02488759 and NCT02643303).

Interesting results come from the evaluation of utomilumab, a human IgG2 agonist monoclonal antibody that showed a favourable response in 2 patients with advanced MCC who achieved a CR (one patient) and a PR (the other) with a DoR > 6 and 22 months, respectively (Segal et al. 2018).

Finally, combinations of immunotherapeutic options are being evaluating (NCT02584829, NCT03212404 and NCT03000257)(See Table 2).

Patients who develop resistance or escape to immunotherapy

Despite high antitumour activity of antibodies directed against PD-1 immune checkpoint, resistance to this therapy is frequent due to the activation of adaptive resistance, with upregulation of alternative immune checkpoints. A recent study demonstrated that the upregulation of T-cell immunoglobulin muscin-3 (TIM-3) was associated with anti-PD-1 resistance, and the inhibition of TIM-reverted the resistance to anti-PD1 antibodies in a mouse model of lung adenocarcinoma (Koyama et al. 2016).

On the other hand, a possible mechanism of escape from immunotherapy is the loss of classical and non-classical major histocompatibility complex molecules impairing adaptative and innate immune responses (Ritter et al. 2016), that can be reversed by interferon or epigenetic modulation (Terheyden and Becker 2017).

Radiotherapy and interferon have been demonstrated to release tumour antigens and reverse immune escape mechanisms such as the downregulation of major histocompatibility complex 1, in patients with MCC (Paulson et al. 2014).

Rechallenge after discontinuation

The efficacy of ICI for the advanced MCC setting and the limited therapeutic options after progression raise the question if patients previously treated with these drugs, who experience a progression, can be retreated with the same or different agents, after discontinuation (Saleh et al. 2018).

To date, no available data exist for patients with MCC. However, some information on the rechallenge with targeted therapies is available for patients with other endocrine tumours (Felicetti et al. 2017). In advanced melanoma, a clinical benefit has been shown after discontinuation of nivolumab and following rechallenge (Long et al. 2017), with sustained PR (Lipson et al. 2013). However, in a recent case series, the rechallenge with anti-PD-1 was associated with a progressive disease (Martini et al. 2017), while Blasig et al. reported a good response in a series of eight patients, with a SD in three patients and a PR in one patient (Blasig et al. 2017).

Anyway, the development of resistance to any anti-PD1/PD-L1 may lead to resistance to other agents with the same mechanism of action.

Chemotherapy

Due to the effective role of immunotherapy and the reduced risk of side effects, in the next years chemotherapy will remain an option only for those patients with metastatic MCC who are not candidates for immunotherapy or show a progression after immunotherapy. Furthermore, chemotherapy may be reserved for metastatic MCC patients with high tumour burden, acute tumour related symptoms and a good performance status, requiring a fast response.

The impact of chemotherapy on the expression of PD-L1 and PD-1 in cell lines has already been investigated, with different results depending on the experimental model and the chemotherapeutic agent investigated (Chacon et al. 2016; Ghebeh et al. 2010; Peng et al. 2015; Zhang et al. 2008). A recent study evaluated the expression of PD-L1/PD1 in tumour and immune cells of lung cancer after platinum-based chemotherapy, showing that neoadjuvant chemotherapy decreases PD-L1 expression of tumour cells, but not of immune cells, requiring a re-evaluation of PD-L1 expression before immunotherapy (Rojkó et al. 2018). In addition, a significant downregulation of PD-L1 expression with cisplatin–gemcitabine regimen and a tendency to upregulation with carboplatin–paclitaxel regimen, was reported.

In line with Rojkò et al. results, Sheng et al. and Zhang et al. have shown that neoadjuvant chemotherapy induces resistance to immunotherapy, decreasing PD-L1 expression in patients with NSCLC (Sheng et al. 2016; Zhang et al. 2016).

Interesting results from a study on patients with Hodgkin lymphoma treated with chemotherapy alone after PD with ICI showed a 46% of CR, supporting the hypothesis that immunotherapy may sometimes re-sensitize patient response to chemotherapy (Rossi et al. 2018), even though further studies are needed to confirm these results.

Currently, however, no data are available on the use of chemotherapy after immunotherapy in MCC, even though the combination of these agents is being evaluating (NCT 03167164) (See Table 2).

Immunotherapy in patients excluded from clinical trials

The safety and efficacy of anti-PD-1/PD-L1 therapy has been investigated in several clinical trials. However, some conditions often associated to a higher incidence of MCC, such as organ transplantation, HIV infection, active autoimmune diseases, and hematologic or solid malignancies, are commonly considered as exclusion criteria for clinical trials patient's enrollment. Therefore, little experience exists in this setting, except for clinical case reports and small cohort studies.

Autoimmune toxicity represents the most frequent side effect of ICIs, as a consequence of T cells activation against host tissue. For this reason, subjects with autoimmune diseases were excluded from clinical trials, as the further immune stimulation produced by ICIs could lead to an exacerbation of autoimmune disorders and related symptoms (Khan et al. 2016). An interesting study on 52 patients with melanoma and preexisting autoimmune disease showed that treatment with anti-PD 1 triggered autoimmune flare in 30% of patients, resulting in 4% treatment discontinuations, and caused immune related adverse events (irAEs) in another 29% of them, leading to therapy interruption with a rate of 8%. In this cohort, treatment with anti-PD 1 was effective only in one-third of patients (Johnson et al. 2016). In another retrospective study on 41 patients with advanced melanoma and preexisting autoimmune disorders or ipilimumab-induced autoimmune toxicity, 8 patients experienced a flare of autoimmune disease, requiring immunosuppressive therapy (Johnson et al. 2016).

Traditionally, recipients of solid or hematologic stem cells transplants are treated with immunosuppressive drugs to maintain allograft tolerance and to prevent graft versus host disease (GVHD). However, chronic immunosuppression represents a risk factor for the development of a wide spectrum of malignancies, such as MCC (Engels et al. 2011). Despite the increasing need for effective cancer treatments, ICIs are currently contraindicated in organ transplanted patients, because of the higher risk of organ rejection. Accordingly, preclinical data suggested that PD1/PD-L1 could be mainly involved in organ tolerance and that blockage of the PD-1 pathway may lead to an increased organ transplant rejection rate (Terawaki et al. 2007; Herz et al. 2016). Conversely, ICIs have been used in patients following hematopoietic stem cells transplantion without experiencing a higher rate of side effects (Angenendt et al. 2016; Villasboas et al. 2016; Yared et al. 2016). Immunotherapy was also used as a salvage therapy in different transplanted patients, but organ rejection has been frequent in this setting (Barnett et al. 2017; De Toni and Gerbes 2017; Kittai et al. 2017). Fourteen patients who received liver transplant were treated by different ICIs and liver graft rejection was reported in four of them, in 3 cases with lethal outcome. A review of 12 case reports of transplanted patients (9 kidney transplants, 2 liver transplants and 1 heart transplant) treated by anti CTLA 4 or anti PD-1 therapy, mostly for melanoma (7 patients), confirmed a high incidence of graft rejection. Indeed 4 patients, all after kidney transplant, developed a definitive organ rejection. However, 8 patients experienced a PR or SD (duration of response between 4 months and 2,5 years). Kidney transplant was associated to a higher incidence of graft rejection, while a longer time elapsed since transplantation was associated with a higher tolerance (Kittai et al. 2017).

HIV positive patients represent another category of patients for whom ICIs are considered contraindicated, due to the risk of exacerbating the infection or to develop irAEs. In a case series including 10 patients with HIV infection, on antiretroviral therapy, the use of ICIs (3 patients treated with pembrolizumab, 1 with nivolumab, 3 with ipilimumab, and 3 with ipilimumab and nivolumab) for advanced melanoma (9 patients) and MCC (1 patient) did not significantly affect the viral load. Treated patients experienced one CR and one PR among patients treated for melanoma, and a CR in the patient treated for MCC. Toxicities were represented by irAEs in 50% of patients, which were severe in 2 cases (colitis and myositis) leading to treatment discontinuation (Heppt et al. 2017). Another case report showed a CR in a 88-year-old, HIV-infected patients, treated with avelumab for MCC resistant to chemotherapy and radiotherapy. At the time of the publication, the patient received ten administrations of avelumab and experienced hypothyroidism due to an autoimmune thyroiditis (Al Homsi et al. 2018). Even though it is a clinical case-based evidence, ICIs seem to display the same efficacy in HIV positive patients.

Patients with HBV and HCV infections were also excluded from clinical trials. A retrospective study showed that pembrolizumab (2 patients) and nivolumab (5 patients) were safely used also in these patients for the treatment of melanoma or of NSCLC. Only one patient experienced a grade 2 liver toxicity (according to CTCAEs), treated with ledipasvir and sofosbuvir. Two patients experienced a PR and 2 patients a durable SD, still ongoing at the time of publication. However, patients with active hepatitis require a close hepatologic monitoring during treatment (Kothapalli and Khattak 2018).

ICIs, as monoclonal antibodies, are metabolized by circulating fagocitic cells and do not undergo hepatic or renal clearance, thus liver or renal failure do not represent treatment contraindications (Mould and Sweeney 2007). However, patients with severe renal, liver or cardiac dysfunction were excluded from clinical trials. Kanz et al. treated with anti PD-1/PD-L1 27 patients with renal (creatinine ≥ 2 mg/dl or creatinine clearance < 30 ml/min), hepatic (AST, ALT or bilirubine $\geq 3 \times$ upper limit) or cardiac (ejection fraction $< 45\%$) dysfunction, showing a similar incidence and kind of adverse events and a durable response in several patients (Kanz et al. 2016). Similar results were reported by other studies (El-Khoueiry et al. 2017; Rosenberg et al. 2016).

Finally, a recent phase II trial assessed the efficacy of pembrolizumab in patients with untreated or progressing brain metastases from melanoma or NSCLC (18 patients). Data showed the efficacy of pembrolizumab on brain metastases in 33% of patients, with a CR in 4 patients and a PR in 2 patients. Treatment was well tolerated with grade ≤ 2 neurologic toxicity (Goldberg et al. 2016).

Summarizing, ICIs demonstrated a good safety and efficacy profile also in patients classically excluded from clinical trials, suggesting that these treatments could be safely used also in these patients, that are representative of the "real world". Organ transplanted patients represent an exception, due to the high risk of organ rejection. However, larger prospective studies could better investigate this issue.

How long should treatment with immune checkpoint inhibitors be prolonged after complete response?

According to the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO), as well as to the summaries of product characteristics, avelumab and pembrolizumab should be administrated until disease progression or unacceptable toxicity (Brahmer et al. 2018; Haanen et al. 2018; BAVENCIO RCP 2018;

KEYTRUDA RCP 2018), but in the real-life clinical practice the optimal duration of ICIs therapy is still unknown. In particular, few data are available regarding the ideal duration of therapy with avelumab in MCC in cases of complete response (CR). In a recent multicentre, single-group, open-label, phase II trial, complete responders were treated for a minimum of 6 months till a maximum of 12 months, after CR detection, based on investigator's discretion (Kaufman et al. 2016).

However, some evidence is already available about two anti-PD-1 ICIs (nivolumab and pembrolizumab) especially for patients with advanced melanoma. In a randomized, controlled, phase III study (Robert et al. 2015) the administration of pembrolizumab or ipilimumab was arbitrarily stopped after 2 years of treatment, without any specific evidence supporting that. The KEYNOTE-001 study report (Robert et al. 2016), published in 2016, showed a CR in 95 patients with advanced melanoma treated with pembrolizumab. Among these, 61 patients discontinued therapy because of CR and two of them relapsed after discontinuation. In 2017, a retrospective review of CR to PD-1 based therapy in patients with metastatic melanoma was published (Ladwa and Atkinson 2017). The authors investigated two groups of patients treated with pembrolizumab (the Pembrolizumab Named Patient Program [PEM NPP, $N=20$] and reimbursed Pembrolizumab [r PEM, $N=3$]), and one group treated with nivolumab monotherapy (the NIVO, $N=6$). Among these patients that discontinued the treatment because of CR, 3 relapsed at a median follow-up of 8 months. The main limitations of this study are the small number of patients and the short follow-up after discontinuation (10 months in PEM NPP, 4.5 months in PEM, and 9 months in NIVO). However, the interesting aspect is that all the patients who had relapsed were successfully retreated with immunotherapy (Ladwa and Atkinson 2017). A recent report from the KEYNOTE-006 study, which was presented at the 2018 ASCO Congress (Long et al. 2018), evaluated the 4-year OS, PFS, and clinical outcomes in patients with ipilimumab-naive advanced melanoma treated with ipilimumab or pembrolizumab for 2 years. Pembrolizumab performed better than ipilimumab in terms of OS, PFS and duration of response, and after 4 years of follow-up it continues to provide durable antitumour activity (Long et al. 2018). Moreover, the rechallenge with ICIs upon disease progression can provide additional antitumour activity with acceptable safety (Ladwa and Atkinson 2017; Long et al. 2018).

Besides costs, another issue to take into account for ICIs is the treatment-related toxicity, especially because MCC mainly affects the elderly. Avelumab was found to be well tolerated (Kelly et al. 2018) especially if compared to chemotherapy, however, no data are available regarding the safety of long-term therapies.

In conclusion, it could be speculated that prolonging therapy with ICIs beyond 24 months in patients with CR may be not required, considering costs, the potential toxicity, and the possibility to retreat successfully the patients.

What follow-up should be performed during treatment and after complete response?

About the timing of follow-up, the NCCN Clinical Practice guidelines recommend physical exam with complete skin and lymph node evaluation every 3–6 months for the first 3 years after diagnosis, and every 6–12 months thereafter, although individuals at high risk of recurrence (e.g. immunosuppressed patients) should deserve more frequent follow-up (Bichakjian et al. 2018).

The follow-up of these patients should also include the screening of irAEs of ICIs, which most commonly affect the skin, the gastrointestinal tract, the liver, and the endocrine system, although other organs may also be affected (Postow 2015a, b; Boutros et al. 2016). Particularly, endocrine irAEs include hypothyroidism/hyperthyroidism, hypophysitis and autoimmune insulin-dependent diabetes mellitus, with a toxicity which is potentially irreversible (Orlov et al. 2015).

For ipilimumab, nivolumab and pembrolizumab studies in melanoma patients, the median time to onset of moderate to severe endocrine irAEs was 2–5 months after the initiation of therapy (Weber et al. 2013; Faje et al. 2014; OPDIVO RCP 2018; KEYTRUDA RCP 2018), but toxicity can appear even beyond the final dose of treatment, which makes it necessary to continue follow-up for several months after cessation of treatment.

To identify and quantify regional and distant metastases after CR, the NCCN guidelines for MCC recommend contrast-enhanced brain MRI and contrast-enhanced neck/chest/abdomen/pelvis CT or whole body ^{18}FDG PET/CT (Bichakjian et al. 2018). Some studies indicated that both whole body ^{18}FDG PET/CT and ^{68}Ga-somatostatin analogue PET/CT can be useful for monitoring the response of metastases of MCC to active immunotherapy (Eshghi et al. 2018; Taralli et al. 2018).

Conclusions and future perspectives

The development of ICIs has recently revolutionised the clinical management and the prognosis of MCC. Paradoxically, however, many of the patients at higher risk of developing this rare, albeit highly aggressive neuroendocrine tumour seem to be excluded from the possibility to be treated with ICIs.

Several questions on the treatment of patients with MCC are still unresolved. In this manuscript, we tried to deal with some of the most relevant unanswered issues on this topic. However, many other aspects are already facing out on the horizon. What is the role of the disease mutational burden on the response to immunotherapy? Can immunomodulatory agents (e.g. somatostatin analogues) or the combination with radiotherapy help ICIs modulating lymphocyte response of the disease? Should the dose of ICIs be modulated according to the patient characteristics or does a single dose fits all? Will precision medicine help us finding the least toxic and/or most effective drug/dose to tailor the individual patient with MCC? Will the findings of ICIs on MCC pave the way for similar achievements in some other neuroendocrine tumours?

Indeed, preliminary data from the multicohort phase 1b KEYNOTE-28 study (NCT02054806) already showed promising results with pembrolizumab in heavily pretreated patients with PD-L1 positive carcinoid tumours and with well- or moderately differentiated pancreatic neuroendocrine tumours (Menhert et al. 2017).

The therapeutic landscape of neuroendocrine tumours, and in particular of MCC, is rapidly evolving: many open issues will probably be resolved, and many other questions are likely to arise in the next few years. The results of ongoing prospective clinical trials and of several other studies on these issues are eagerly awaited. In the meanwhile, it is reasonable to expect that some other answers to these open issues will not be late.

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