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Overview

Merkel Cell Carcinoma – Current Controversies and Future Directions

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Abstract

Merkel cell carcinoma is a rare, aggressive neuroendocrine skin malignancy. Evidence for management comes from case series and single-arm trials. Optimal outcomes require assessment of the patient in a multidisciplinary team setting. Rapid diagnosis and staging are essential for locoregional control and may reduce metastasis. Sentinel lymph node biopsy (SLNB) adds prognostic information. FDG-positron emission tomography has high sensitivity and specificity and affects management in a quarter of cases. Surgical excision and radiotherapy provide good locoregional control even with positive margins. Wide surgical margins are needed if adjuvant radiotherapy is not used. It is uncertain whether adjuvant radiotherapy or elective surgery for uninvolved nodes or for patients selected by positive SLNB improves survival. Total doses of 50 Gy provide high levels of control for microscopic disease but at least 60 Gy should be given for macroscopic disease. Chemotherapy can be given safely with radiotherapy, but the benefit of adjuvant chemotherapy remains uncertain. Trials of adjuvant immune therapy are underway. Unresectable primaries might be controlled with radiotherapy alone or combination systemic therapy, radiotherapy and surgery. Metastatic disease often responds to chemotherapy, but the response duration can be short. Immunity is central to disease control. Immune checkpoint inhibitor treatment resulted in high response rates in chemotherapy-naive patients and lower rates in chemotherapy-refractory patients. Durable responses are observed.

Key words: Immune checkpoint inhibition; Merkel cell carcinoma; radiotherapy; surgery

Introduction

Merkel cell carcinoma (MCC) is a rare high-grade, locally invasive, highly metastatic neuroendocrine skin cancer [1,2]. The incidence in England rose between 1998 and 2008 from 0.1 to 0.2/100 000 (total 1515 reported cases) [3], similar to the European Union, with age-adjusted incidence rates <0.1 (<24 years), 0.35 (25–64 years) and 7.3/million (65 years or older) [4]. North American and Australian data indicate rates of 0.79 and 1.6/100 000, respectively (reviewed in [5]).

Exposure to ultraviolet light, immunosuppression and advancing age are known risk factors. Merkel cell virus (MCV) is a common skin commensal. In many cases of MCC, it is integrated into the malignant genome, resulting in loss of replicative competence and expression of small and truncated large T (sT and LT) antigens, which interact with multiple cellular targets. Disrupted pathways include protein translation, promotion of motility, indirect p53 inactivation, promotion of replication and altered gene expression by RB1 binding (reviewed in [6]). MCV-negative MCC are more likely than virus-positive tumours to present on light-exposed parts of the body and have a higher mutation burden, including ultraviolet light signature mutations and somatic copy number alterations [7]. Immunogenicity is driven by MCV expressing antigens or by ultraviolet light mutagenesis generating neoantigens in MCV-negative MCC [7–9]. The centrality of immunity to MCC biology should inform the development, selection and optimisation of management strategies.

The presentation and natural history of MCC is described in an analysis of more than 14 000 cases in a large registry in the USA [10]. Standard management of MCC is focused around the use of surgery and radiotherapy for primary and nodal metastases, and cytotoxic chemotherapy and immune checkpoint inhibitors (CPI) for unresectable and metastatic disease [11]. This review updates the previous excellent review in *Clinical Oncology* [12], including

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discussion of the relevance of MCC viral and immune biology to management and developments in systemic therapy.

Clinical Presentation, Pathology, Staging and Prognosis

Patients most frequently present with a history of a rapidly enlarging painless skin lesion. MCC has a characteristic smooth purplish appearance but its unfamiliarity, and absence of typical sinister features for skin cancer, mean referral delays are common. About 10% of patients present with nodal metastases and an unknown primary. Pathological diagnosis is critical as clinical diagnosis is unreliable. Once MCC is suspected, patients must be managed urgently as tumours may grow rapidly.

Histological diagnosis of primary MCC and baseline staging are key to guiding management and providing estimates of prognosis. The diagnostic microscopic features are small blue cells with high mitosis and apoptosis, CK20 perinuclear dot staining, immunohistochemical markers of neuroendocrine differentiation (synaptophysin and chromogranin), co-expression of cytokeratins and neurofilament, absence of lymphoid and melanoma markers and exclusion of lung small cell carcinoma by thyroid transcription factor negativity. Combined MCC tumours (usually with squamous cell carcinoma), CK20-negative MCC and those associated with markers of sun damage are more likely to be virus-negative [13]. Using a combined modality approach to MCV detection (requiring demonstration of MCV LT by at least two of quantitative polymerase chain reaction and immunohistochemistry using CM2B4 and Ab3 antibodies), about one-fifth of MCC in a US cohort were virus-negative and these were associated with a poorer outcome. A CM2B4 antibody test alone appeared a reasonable approach for routine clinical use [14]. In an experimental approach, detection of circulating antibodies against MCV T oncoproteins at presentation and falling titres after treatment were each associated with better outcomes [15].

European and US guidelines advise the use of sentinel lymph node biopsy (SLNB) to provide more accurate prognostication of patients presenting without clinically or radiological evidence of nodal involvement [11,16]. Occult disease can be found in clinically negative nodes in 24% of MCC patients [17]. In a review of published retrospective series, positive sentinel nodes were detected in 30% of cases and the false-negative rate was 17% [18]. A positive SLNB was associated with larger primary size and presence of lymphovascular invasion, but a threshold primary size below which SNLB is typically negative is not apparent [19]. Sentinel lymph node mapping without biopsy can give valuable information regarding lymphatic drainage for primary tumours located in sites that may drain to multiple basins or midline lesions that may drain bilaterally [20].

Baseline staging should include cross-sectional imaging of the thorax, abdomen and pelvis and include neck nodes for tumours in the head and neck region. A recent systematic review of FDG-positron emission tomography (FDG-PET) in MCC suggests that PET has a high sensitivity of 90% and a specificity of 98% in the detection of MCC [21]. In a prospective Australian study, PET had high positive and negative predictive values for detecting MCC and changed decision-making in over a quarter of patients, upstaging patients through the detection of regional or distant metastases not apparent on contrast computed tomography [22]. In a retrospective study, PET detected occult nodal involvement in only 3/21 patients with positive SLNB, suggesting that it does not replace SLNB in staging [23].

No standard follow-up imaging strategy is recognised, but if routine scanning is offered, it is logically positioned across the first 2 years after definitive treatment because the median time to recurrence is 8 months and 90% occur by 24 months [1]. In a retrospective series of 37 patients, a complete metabolic response (CMR) on PET scanning, undertaken at a median 3.5 months after definitive treatment, appeared to be prognostic: contrasting the 2-year survival rate of 86% (CMR) with the 1-year survival rate of 15% (no CMR) [24].

Prognosis

The Union for International Cancer Control (UICC) TNM8 staging system for MCC [25], almost identical to the American Joint Committee on Cancer (AJCC) eighth edition [10], was implemented in the UK in 2018 (Tables 1 and 2). They provide pathological and clinical prognostic categorisation separately according to the use of SLNB, which upstages patients with occult nodal metastases at presentation. Five-year survival for primary MCC without detectable nodal spread ranges from 63% to 35% with SLNB, dependent on tumour staging, and from 45% to 27% for the more heterogeneous group without SLNB. For patients presenting with regional disease, stage IIIA groups together those with pathological detection of occult nodes (N1a) with those presenting with nodal disease and unknown primary (T0N1b). Stage IIIB includes clinically apparent primary plus nodes (T1-4N1b), in-transit metastases (N2) or both (N3). Five-year survival proportions for patients presenting with stage IIIA and IIIB are 40% and 27%, respectively. Presentation with distant metastases results in a 14% 5-year survival [10].

Treatment of Primary Merkel Cell Carcinoma

The evidence for treating MCC is confounded by the paucity of randomised trials or coherent prospective data. A systematic review of case series and reports, comprising 418 patients stage I–IV undergoing various surgical modalities, reported 1- and 5-year local relapse-free survival of 70.5% and 60.5%, respectively [26]. This has been supported in more recent case series [27,28]. A review of 6401 MCC cases in the SEER database observed better survival of patients with wider margins (>2 cm and 1–2 cm compared with <1 cm). Independence of surgical margin from other variables

Table 1
TNM eighth edition staging for Merkel cell carcinoma [10]

Tx	Primary tumour cannot be assessed (e.g. curetted and no clinical dimension recorded)
T0	No evidence of primary tumour (e.g. nodal/metastatic presentation without associated primary)
Tis	*In situ* primary tumour
T1	≤20 mm maximum clinical dimension of tumour
T2	>20 mm to ≤50 mm maximum clinical dimension of tumour
T3	>50 mm maximum clinical dimension of tumour
T4	Primary tumour invades fascia, muscle, bone or cartilage (i.e. beyond subcutaneous fat)
cNx*	Regional lymph nodes cannot be clinically assessed (e.g. previously removed for another reason, body habitus)
cN0	No regional lymph node metastasis by clinical or radiological evaluation
cN1	Clinically detected regional nodal metastasis
cN2	In-transit metastasis without lymph node metastasis
cN3	In-transit metastasis with lymph node metastasis
pNx†	Regional lymph nodes cannot be assessed (e.g. previously removed for another reason) or not removed for pathological evaluation
pN0	No regional lymph node metastasis detected on pathological evaluation
pN1a(sn)	Clinically occult nodal metastasis identified only by sentinel lymph node biopsy
pN1a	Clinically occult regional lymph node metastasis following lymph node dissection
pN1b	Clinically or radiologically detected regional lymph node metastasis, pathologically confirmed
pN2	In-transit metastasis without lymph node metastasis
pN3	In-transit metastasis with lymph node metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis to distant skin, distant subcutaneous tissue or distant lymph nodes
M1b	Metastasis to lung
M1c	Metastasis to any other distant site

* Clinical staging is defined by clinical and radiological evaluation for metastasis.
† Pathological staging requires sentinel lymph node mapping or nodal dissection.

Table 2
Eighth edition American Joint Committee on Cancer staging system and outcomes from 9387 patients [10]

Clinical staging*					Pathological staging†				
Stage	T	N	M	5-year overall survival	Stage	T	N	M	5-year overall survival
0	Tis	N0	M0		0	Tis	N0	M0	
I	T1	N0	M0	45.0%	I	T1	N0	M0	62.8%
IIA	T2-3	N0	M0	30.9%	IIA	T2-3	N0	M0	54.6%
IIB	T4	N0	M0	27.3%	IIB	T4	N0	M0	34.8%
					IIIA	T1-4	N1a(sn) or N1a	M0	40.3%
						T0	N1b		
III	T0-4	N1-3	M0		IIIB	T1-4	N1b-3	M0	37.5%
					IV	T0-4	Any N	M1	13.5%

* Clinical staging is defined by clinical and radiological evaluation for metastasis.
† Pathological staging requires sentinel lymph node mapping or nodal dissection.

was not tested, but in multivariate analysis, outcomes for surgery, irrespective of margin, were better than for local destruction, i.e. photodynamic therapy, electrocautery, fulguration, cryosurgery, laser ablation, excisional biopsy [29].

Excellent local disease control (96.4%) has been reported using surgery and adjuvant radiotherapy to the primary [30]. A systemic review of retrospective series reported 1- and 5-year local relapse-free survival of 90.5% and 87.9%, respectively, for 169 patients undergoing mixed surgical modalities plus adjuvant radiotherapy to the tumour bed [26], with similarly high local control rates in more recent series [28,31,32]. This has been reinforced by a multivariate analysis of nearly 5000 patients presenting with stage I–III MCC in the US National Cancer Database, demonstrating a 29% and 23% reduction in hazard of death with adjuvant radiotherapy for stage I and II MCC, respectively [33].

Radical radiotherapy for primary MCC has been shown in small series to be an effective treatment in some patients. Local control rates for definitive radiation vary from 75% to >90% [31,32,34,35]. A review of National Cancer Database MCC data on stage I–III cases identified 1227 listed as having definitive radiotherapy and matched these with 1227 patients who had undergone surgery, although treatment details were lacking for both groups. Definitive radiotherapy versus surgery was associated with survival at 5 years in 32% and 61% (stage I and II) and 19% and 34% (stage III), respectively. Differences in socioeconomic

variables, tumour size and time to treatment favoured the surgically treated patients. Furthermore, the data lacked granularity, particularly on whether definitive radiotherapy was after local excision biopsy or for macroscopic disease, on the margins defining definitive surgery and on locoregional control rates for each treatment approach [36]. In multivariate analysis of SEER data, better survival, although not cancer-specific survival, was observed for patients receiving radiotherapy and who had surgery rather than other local destruction modalities [29]. Although these data may indicate that surgery with radiotherapy delivers better outcomes than radiotherapy alone, this evidence is not definitive without controlling for confounding factors.

For most early stage MCC, the primary is removed surgically to obtain a histological diagnosis. Based on this limited evidence, it is reasonable to offer at least excision with primary closure plus radiation for most primary MCC and reserve definitive radiation treatment without excision of the primary for if the patient is medically inoperable or if resection would have an adverse effect on function and cosmesis. If the primary site is to be managed with surgery alone, margins should be wide.

Surgery and Radiotherapy for Nodal Disease

Without SLNB there is some evidence to suggest that nodal control is improved by adjuvant radiation to the nodes. A prospective randomised trial in 83 patients with primary MCC without macroscopic nodal involvement, randomised to receive adjuvant nodal radiotherapy or not, closed early because of the increasing use of SLNB in the trial population. The probability of regional recurrence was lower in the intervention arm (0% versus 16.7%), there was a possible 3-year progression-free survival (PFS) benefit (89.7% versus 81.2%, $P = 0.4$) but no hint of gains in overall survival [30].

Regarding patients who do undergo SLNB, in collated retrospective studies, 93% of SLNB-positive and 8% of SLNB-negative patients underwent nodal irradiation and the nodal recurrence rate was around 10% for both groups. A higher proportion of SLNB-positive than SLNB-negative patients suffered distant relapse (18% versus 7%) [18]. In retrospective studies, the outcomes of completion nodal dissection for SLNB-positive MCC were similar to nodal irradiation [37,38]. However, randomised trials would be needed to determine whether SLNB-directed therapy prolongs survival compared with clinical and radiological staging with follow-up, and whether one modality (radiotherapy versus completion nodal dissection) out-performs the other for SLNB-positive patients in regional control and toxicity.

For patients presenting with nodal involvement, small series indicate that either nodal dissection or irradiation are potentially effective [37]. A meta-analysis of >2000 stage III patients in the National Cancer Database did not detect a survival benefit for either adjuvant chemotherapy or for surgery plus radiotherapy compared with surgery alone [33].

Radiotherapy Technique

Radiotherapy should be delivered to the skin primary with a wide margin. For adjuvant treatment, the clinical target volume should be based on clinical assessment of the excision site, operation notes, histopathology report and preoperative clinical photographs. The clinical target volume depth should be to the fascial plane on planning computed tomography or by palpation. For most MCC patients, it is possible to give radiotherapy with a direct electron radiotherapy field, but for larger tumours in difficult sites, more complex techniques may be needed to spare adjacent critical normal structures, e.g. intensity-modulated radiotherapy (IMRT), rotational arc therapy, e.g. volumetric modulated radiation treatment (VMAT) or tomotherapy. Wide margins, e.g. 3 cm, should be given wherever feasible, but in some sites, e.g. close to the eye, a narrower margin of 1 cm is acceptable.

The radiotherapy technique for involved nodal fields will depend on the primary and nodal sites. In the head and neck, the primary tumour and involved nodes might be treated as a single volume with IMRT to minimise doses to normal structures. For axillary or inguinal nodes, the nodal volume should be contoured and planned with appropriate radiotherapy field arrangements.

MCC tumours may shrink during radiotherapy, sometimes requiring repeat planning if the set-up is no longer reproducible. Therefore, for large rapidly growing tumours, a rapid start to radiotherapy with simple field arrangements might be prioritised. Several studies have confirmed that total doses of 50 Gy (given as daily 2 Gy fractions) for microscopic disease and total doses of 60–66 Gy (given as 2 Gy daily fractions) can achieve high rates of local tumour control [27–29]. These dose schedules can also be used for nodal radiotherapy in the head and neck region, but for axillary and inguinal nodal regions the total radiotherapy doses should not be above 50 Gy total dose (2 Gy per fraction) due to the risk of brachial plexopathy or severe lymphoedema. Multivariate analysis of >2000 National Cancer Database patients given adjuvant radiotherapy for stage I–III trunk and limb MCC indicated that a dose range <40 Gy was associated with poorer survival accounting for other factors [39].

Chemotherapy for Locoregional Merkel Cell Carcinoma

Chemotherapy has been investigated as part of definitive treatment for locoregional MCC at high risk of recurrence in a prospective Australian phase II study. Radiotherapy was given to the primary site, in-transit areas and draining nodes at a dose of 50 Gy in 25 fractions over 5 weeks to macroscopic disease or the operative site or 45 Gy to clinically uninvolved areas. Carboplatin AUC 4.5 and etoposide

80 mg/m^2 intravenously days 1–3 was given concurrently and after radiotherapy to four cycles. The 3-year relapse-free survival was 65% and distant control was 76% in this high-risk population. Nodal disease was associated with poorer survival, but gross residual disease before chemo-radiotherapy did not affect the probability of locoregional control or survival [40]. A subsequent trial in patients selected as stage IIA to IIIB or with recurrence using computed tomography-PET at screening gave 76% 3-year survival, 89% 3-year in-field locoregional control and 70% 3-year distant control [22]. Chemotherapy has a role as part of multimodality definitive treatment for challenging MCC locoregional disease but a routine role as adjuvant therapy would have to be defined in a randomised trial.

Systemic Therapy for Unresectable and Metastatic Disease

Widely used chemotherapy regimens are those developed for other small cell cancers: cyclophosphamide, doxorubicin (or epirubicin) and vincristine (CAV or CEV) and carboplatin (or cisplatin) and etoposide (EP). Response rates around 29–75% and complete response rates of between 13 and 35% have been reported [41–43]. There are also signals of activity for taxanes and irinotecan [44]. The durability of benefit from first-line chemotherapy is highly variable: in a retrospective series, PFS in 26 patients achieving a partial response ranged from under 4 weeks to nearly 2 years with a median of 21 weeks, meaning that nearly half were progressing before the completion of a nominal six 3-weekly cycles. For eight patients with complete responses, PFS ranged from 20 weeks to over 2 years [42]. A short median duration of response and PFS has been observed in other studies [43]. Both immune-competent and immune-suppressed patients are reported among those benefiting from chemotherapy. Thirty patients were reported as having second-line chemotherapy, with a 23% response rate mainly to CAV, a single complete responder and a median PFS of nearly 9 weeks but ranging up to nearly a year. Topotecan and paclitaxel were most commonly used but without responses [42]. A series of patients undergoing third-line chemotherapy using variable regimens after prior progression showed a response rate of under 10% with no complete responses [45].

The use of monoclonal antibody immune CPI for patients with unresectable or metastatic MCC, excluding those with known immune deficiency or treated for autoimmune diseases, has been investigated in small single-arm prospective trials. In patients naïve to systemic therapy, the use of anti-PD1, pembrolizumab, resulted in an objective response rate of 56%, 48% PFS and 69% survival at 24 months. Responders included those with both MCPyV-positive and -negative tumours. The PD-L1 status of the tumour was associated more with viral positivity but neither PD-L1 positivity nor prior CD8-positive infiltrate in the tumour predicted response [46,47]. In a similar population, the PD-L1 inhibitory monoclonal antibody, avelumab, gave a response rate of 62% with >80% ongoing at 6 months [48]. In a trial for patients who had progressed on previous chemotherapy, including 41% with more than one line of previous treatment, the overall response rate to avelumab was 33%, durable (>6 months) response rate 29% and complete response rate 9%. Three-quarters of responses lasted more than 1 year. The response was not clearly associated with tumour viral or PD-L1 status [49,50]. The activity of anti-CTLA4, ipilimumab, is reported only in case series and its activity cannot be clearly separated from previous or concurrent radiotherapy or subsequent anti-PD-1 [51]. A trial including MCC cohorts treated with anti-PD-1 nivolumab alone or with ipilimumab is ongoing (NCT02488759). Although CPI target key regulatory mechanisms that limit autoimmunity and response to malignancy, other immune modalities might induce new cancer-specific immune responses through exposure of tumour antigens to professional antigen-presenting cells (pAPC). Talimogene laherparepvec (TVEC) is a novel therapy in which human herpes virus, modified to delete neurotropism and express granulocyte macrophage colony stimulating factor, is injected directly into tumours. Oncolysis and antigen release are thought to be linked to pathogen-associated molecular pattern pro-inflammatory signalling and recruitment of pAPC. Isolated cases are reported of MCC responding to TVEC alone or in a patient progressing on anti-PD-1 [52,53]. A phase II trial of TVEC, with or without concurrent radiotherapy, for patients with unresectable skin or nodal MCC is ongoing (NCT02819843). An alternative pathogen-associated molecular pattern-based approach is the reported use of intra-tumoural G100, a potent agonist of Toll-like receptor (TLR) 4 on pAPC, which in turn promotes T_H1-type T cell responses. Outcomes included response in 2/7 patients treated in the palliative context and another with a complete pathological response to neoadjuvant G100 [54]. Single-fraction radiotherapy is well recognised as a palliative treatment for symptomatic MCC lesions with a high chance of response. However, in two cases, radiotherapy given for tumour progression on CPI therapy also resulted in an out-field, abscopal response, suggesting that irradiation at one site altered general immune responsiveness [55]. This concept is being tested in a randomised trial comparing nivolumab and ipilimumab with and without irradiation (NCT03071406). Another approach is to supplement CPI therapy with autologous T cells specific for known MCV peptide targets specific to each individual's major histocompatibility complex genotype. This can cause new intense T cell infiltration into MCC tumours. Late relapse is reported to be associated with transcriptional repression of the relevant major histocompatibility complex in the tumour, a mechanism susceptible to further manipulation [56].

There is currently no defined role for molecularly targeted treatment in advanced MCC. Frequent expression of platelet-derived growth factor (PDGF) and PDGF receptor, vascular endothelial growth factor (VEGF) A and C, VEGF receptor 2 and c-KIT (but without mutations) has been observed in MCC [57–59]. Limited studies report isolated responses to oral multi-targeted tyrosine kinase inhibitors but without selection of agent based on tumour genomic

profiling. Pazopanib inhibits PDGF receptors, VEGF receptors and c-KIT. A patient with advanced MCC who had failed first-line chemotherapy experienced a partial response lasting 6 months in a pazopanib phase I study. A PDGF receptor germline polymorphism was detected, also identified in other MCC cases and the general population [60]. A complete response to imatinib, which targets cKIT and PDGF receptor, has been reported in a patient with overexpressed cKIT but without detectable mutations [61]. A trial of cabozantinib for MCC closed, accruing eight patients, due to lack of efficacy and poor tolerance [62]. MCC, particularly MCV-negative tumours, does harbour genetic aberrations, some of which might be actionable by currently available agents [7,9]. In a recent report, 17 MCC were investigated by next generation sequencing. Most harboured TP53 aberrations and/or alterations in cell cycle regulation, affecting CDKN2A/B, CDKN2C or RB1. Aberrations in the PI3K/AKT/mTOR pathway were detected in over half the samples, affecting DNA repair mechanisms in over a quarter. Many of these pathway aberrations might be specifically targeted by individual matching to available agents [63]. 177Lu-dotatate has been shown to be an effective and safe therapeutic option for somastostatin receptor-expressing neuroendocrine tumours with an overall response rate of 20–30% and minimal toxicity [64]. This is being explored with immunotherapy in an Australian prospective trial.

Conclusions

The management of patients with MCC is built on long experience, not randomised trials. MCC requires speedy and accurate diagnosis and staging for the most suitable locoregional and systemic treatments, which are best carried out by a tertiary multidisciplinary team. Treatment has converged on excision and adjuvant radiotherapy for early stage disease, with wide margins required at least if adjuvant radiotherapy is not planned, giving a good probability of disease control for smaller tumours. The addition of SLNB provides valuable prognostic information and might support selective nodal intervention. Better imaging with FDG-PET has also had an impact on management. IMRT, VMAT and tomotherapy provide greater dose conformity and reduce toxicity to organs at risk, but are unlikely to affect hard end points such as survival. Single-arm clinical trials have led to CPI systemic therapy for metastatic MCC, possibly prioritising this modality over cytotoxic chemotherapy.

Immune CPI therapy is being investigated as adjuvant therapy for stage III MCC in a large phase III trial (NCT03271372) and for stage I and II MCC in a forthcoming trial. CPI treatment may also have a place in the neoadjuvant setting [65]. Importantly, prior CPI trials excluded patients with known immune suppression, who constitute a significant proportion of patients with MCC and who may represent the tip of the iceberg of variable immune dysfunction in an elderly population with an immunogenic tumour. We have scant data about the interactions between a patient's general immune status and standard modalities, surgery, radiotherapy, chemotherapy or CPI therapy.

In summary, treatment for MCC needs to be tailored to the site, stage, patient's fitness and possibly immune status. Immunotherapy trials will help to shape the optimal management of MCC in the future, but surgery and radiotherapy continue to be the prime modalities in achieving locoregional control.

Conflicts of interest

N. Steven provided education to Merck Serono with recompense to the University of Birmingham; M. Poulsen sits on the Merck Serono Merkel Cell Carcinoma Clinical Advisory Board.

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