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Review Article

Navigating Recent Progressions in Merkel Cell Carcinoma

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Abstract



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Merkel Cell Carcinoma (MCC) is a rare and highly aggressive neuroendocrine skin cancer, characterized by rapid growth, early metastasis, and high mortality rates. Despite accounting for less than 1% of all skin cancers worldwide, its aggressive nature and association with immunosuppression, advanced age, UV exposure, and Merkel cell polyomavirus (McPyV) underscore its clinical significance. Modern diagnostic advancements, including sentinel lymph node biopsy and ctDNA assays, improve early detection and monitoring. Immune checkpoint inhibitors, such as avelumab, pembrolizumab, and nivolumab, have revolutionized the therapeutic landscape, delivering durable responses and improved survival. Combination therapies and experimental agents, like Retifanlimab and anti-LAG-3 inhibitors, offer hope for addressing resistant cases. Despite these advances, MCC presents significant challenges, including diagnostic delays, treatment resistance, and immunotherapy-associated toxicities. Chemotherapy remains an option but offers limited and transient benefits compared to immunotherapy. Early detection, advanced molecular profiling, and personalized therapies are crucial for optimizing outcomes. This review provides a comprehensive summary of MCC's clinical and molecular characteristics, current treatment paradigms, and ongoing research, highlighting the pressing need for continued innovation and research. Effective interventions are critical to improving survival rates and addressing the unique challenges posed by this aggressive malignancy.

Keywords: Circulating Tumor DNA (ctDNA), Immunotherapy, Merkel Cell Carcinoma (MCC), Merkel Cell Polyomavirus (McPyV), Sentinel Lymph node biopsy (SLNB).

INTRODUCTION

Merkel Cell Carcinoma (MCC) is an uncommon and aggressive cutaneous neuroendocrine malignancy with significant clinical importance due to its rapid progression, high metastatic potential, and elevated mortality rates. Representing less than 1% of all skin cancers, MCC remains one of the most challenging malignancies to diagnose and treat effectively. The disease predominantly affects individuals with a history of immunosuppression, extensive UV exposure, or those harboring Merkel cell polyomavirus (McPyV), which is implicated in 80% of cases. Additionally, genetic alterations in tumor suppressor genes like TP53 and RB1 further contribute to its pathogenesis.

MCC often presents as a painless, fast-growing nodule on UV-exposed skin, which frequently leads to delayed diagnosis due to its nonspecific presentation. Conventional therapies, including surgical excision and radiation therapy, provide localized control but are often inadequate for advanced stages. Recent breakthroughs in immunotherapy, particularly immune checkpoint inhibitors such as avelumab, pembrolizumab, and nivolumab, have revolutionized treatment, showing remarkable efficacy in achieving durable responses and improved survival rates in metastatic and advanced disease settings. Given MCC's rarity and its aggressive

clinical behavior, there is a critical need for comprehensive reviews to consolidate current knowledge and identify gaps for future research. This article examines MCC's epidemiology, diagnostic techniques, treatment modalities, and the persistent challenges associated with its management. It aims to provide a holistic view of existing therapies while exploring innovative strategies that can further enhance patient outcomes.

DEFINITION

A rare and aggressive cutaneous neuroendocrine cell (Merkel-cell) malignancy¹. Merkel cell carcinoma is distinguished by its quick growth, early metastases² and high death rates^{3,4}.

EPIDEMIOLOGY

The annual incidence of MCC, which is a type of skin cancer, is less than 1% worldwide, with 0.24 cases per 100,000 people in India⁵. Five-year overall survival rate $\leq 18\%$ ⁶. Nodal tissue involvement is 35% and distant metastases are 14%⁷. The prevalence of MCC associated with radiation is 50%, with 37-42% of cases occurring in children and 42% in adults⁸. Forty percent of cases are diagnosed at advanced stages due to the poor prognosis⁹. Virus-positive MCC driven by Fewer mutations; largely driven by viral integration. Virus-

negative MCC with High somatic mutation rates due to UV damage (e.g., mutations in TP53, RB1, NOTCH

pathways)¹⁰.

Table 1 Types of MCC^{11, 12, 13, 14, 15}

CATEGORY	SUBCATEGORY	DESCRIPTION
Causative Factor	MCC associated with viruses	Positive for polyomavirus MCC (McPyV)
	MCC not associated with viruses	Radiation-induced MCC (UV or extended scanning
Histological Variants	Small cell type	Similar to small cell lung cancer
	Trabecular type	Cells with a trabecular pattern
	Intermediate type	Characteristics of small cells type and trabecular type combined
	Spindle cell variant	Long, spindle-shaped cells that resemble sarcoma
Anatomy	Head, neck, trunk, and lymph regions	Primary tumor risk associated with these areas

RISK FACTORS

1. Risk elements Age 75 and up
2. UV radiation exposure
3. Distant metastases and recurrence of other malignancies
4. Viral-polyomavirus
5. Men have a higher incidence or survival rate than women.
6. White and lighter-skinned race and ethnicity
7. Black survival is terrible¹⁶.
8. Immunosuppression is among the comorbid conditions¹⁷.
9. Genetic Predisposition: TP53 or RB1 MATGT1 mutations¹⁸.

ETIOLOGY

In 80% of MCC cases, Merkel cell polyomavirus McPyV is found. The virus integrates into the host's DNA and causes the development of viral onco-proteins, including small and large T-antigens, which disrupt the control of the cell cycle. Inactivation of tumor suppressor proteins, such as PJ3 and RB1, which encourages uncontrolled proliferation of cells¹⁸.

❖ Ultraviolet radiation: Chronic exposure to ultraviolet rays can cause DNA damage and mutations in genes like p53 and RB1, which are important etiological factors for McPyV negative MCC¹⁹.

❖ Immunosuppression-MCC is an invasive skin cancer that has a significant risk of returning, especially in immunocompromised people. It also accounts for 20% of autoimmune diseases, which are caused by both immunological dysregulation and carcinogenic causes.

❖ The TP53 gene and abnormalities in cell cycle pathways have been recognized as genetic changes in MCC²⁰.

❖ Environmental and lifestyle factors: Chronic damage

to the skin from extended UV exposure.

PATHOGENESIS

The Merkel cell polyomavirus is linked to a big T-antigen that recognizes its antiproliferative C-terminal domain while retaining the N-terminal section that inhibits Rb Activation or DNA damage response: ATM and ATR pathways are activated by MCV infection and LT expression, with LT mainly triggering the ATR pathway. By upregulating p53 target genes p21, the C-terminal portion of LT-induced DDR activates p53 and inhibits proliferation. Functional contrasts with SV40: MCV LT activate p53, resulting in gene expression and cell cycle quest, in contrast to sv40 LT, which inhibits P53's transcriptional activity. Effects of the cell cycle While the C-terminal region of MCV LT arrests cells in S-phase and G2/M via DDR/p53 activation, the N-terminal region encourages G1/S progression. In order to encourage viral genome replication, full length LT balances these conflicting effects. The mechanisms of oncogenesis Only after LT truncation mutations, which eliminate the C-terminal antiproliferation does tumorigenesis take place. MCV small T-antigen (ST), which targets 4E-BP7, aids in transformation. MCV-induced DDR activation acts as an anticancer barrier that is broken when mutations permit LT-driven unchecked growth and metastasis [18]. UV-exposed or MCC without a polyomavirus MCC or virus that is not polyomavirus mutations brought on by UV or radiation are linked to negative MCC. Epidermal stem cells, which can also develop into keratinocytes, are most likely the source of MCC. In order to distinguish virus negative MCC (V-MCC) from other types of skin cancer, it must disrupt RB1 through mutations or viral T-antigen sequestration. V-MCC shares genetic characteristics with squamous cell carcinoma and UV-damaged skin, including recurrence mutations in NOTCH, TP53, FAT-1, and HRAS. Interestingly, V-MCC frequently has amplifications or mutations that provide therapeutic targets, indicating the necessity of clinical sequencing. Additionally, similar to melanoma, immune checkpoint blockade therapy may be beneficial for certain V-MCC patients¹⁹.

CLINICAL FEATURES

The AEIOU acronym summarizes the unique clinical features of Merkel cell carcinoma (MCC):

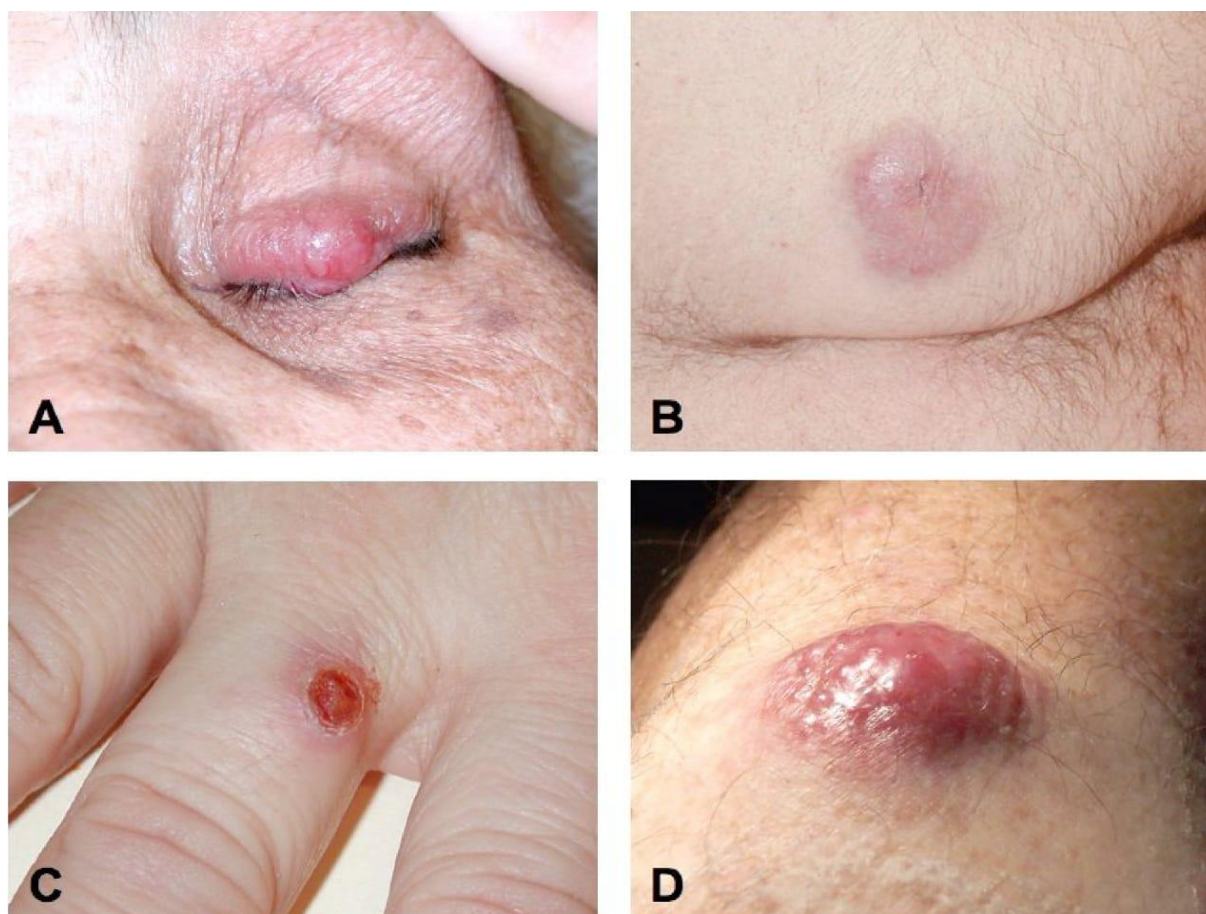


Figure 1 Clinical Presentations of MCC²¹

Lack of symptoms or tenderness: Lesions were painless in 88% of cases. Growing quickly: 63% exhibited strong growth within 3 months inhibition of the immune system: Immunocompromised patients frequently exhibit Over fifty years old: Over 50 UV-exposed sites accounted for 90% of the patients: 81% happened in places exposed to UV light^{22, 23}.

Additional Clinical Features:

Colour: usually violaceous (56% red/pink), pink, blue, or red. usually a bluish-red or flesh-colored lump that is hard and glossy.

Dimensions: 1.8 cm is the median tumor diameter in instances, the initial tumor size varied from less than 1 cm in 21.3%, 1–2 cm in 43.3%, and greater than 2 cm in 35.3%.

Look: One lump or plaque, occasionally resembling a cyst features of Histology

Tiny, spherical cells with plenty of mitoses and sparse cytoplasm. The core granules are dense.

MCC patients frequently misdiagnosed at first (56% assumed benign) most prevalent in older, white (Caucasian) patients²³.

PROGNOSIS

The prognosis for Merkel cell cancer (MCC) varies according on patient-specific variables and improvements in monitoring and diagnostic techniques. Circulating tumor DNA (ctDNA), a less invasive option to regular imaging for surveillance, was found to be very successful in detecting MCC recurrence, minimal residual disease, and disease progression²⁴. Another study emphasized the Merkel cell polyomavirus (MCPyV) antibody test's predictive usefulness, indicating that it may be useful in directing risk assessment and follow-up plans²⁶. The need for individualized treatment strategies was highlighted by the analysis of 762 MCC patients, which showed that those with autoimmune illnesses had an intermediate probability of recurrence when compared to immunocompetent people and those with other immune dysfunctions. In addition, a case-control study on cardiac metastatic MCC investigated treatment and results, emphasizing the necessity of more research into these uncommon manifestations. These findings highlight how important tailored strategies are for controlling MCC prognosis and follow-up.



Figure 2 Additional Clinical Presentations of MCC²⁵

RECURRENCE PROGNOSIS

High Recurrence Risk: High recurrence rate noted, with stage I-IV patients at substantial risk of illness return within 5 years. For patients with positive ctDNA, the recurrence-free probability at 12 months is 9%. For patients with negative ctDNA, the recurrence-free probability at 12 months is 91%.

Patients in Stages I–III:

With an HR of 7.4 [95% CI, 2.7 to 20], ctDNA testing helps differentiate between patients who are at risk for

recurrence and those who are likely to benefit from curative surgery and radiation therapy.

EARLY DIAGNOSIS

Thorough examination of the skin and biopsy of the questionable area 12 Immunohistochemistry (IHC) staining validates the initial H&E staining

Suggested IHC Markers

MCC2 sensitivity of 89–100% for cytokeratin 20 (CK20)

Using thyroid transcription factor-1 (TTF-1), small cell

lung carcinoma is ruled out.²

Other indicators include neuron-specific enolase², chromogranin a, neurofilament protein, synaptophysin, and CD56. Other indicators include neuron-specific enolase, chromogranin A, neurofilament protein, synaptophysin, and CD56.^{26, 27}

CONDITIONS FOR PATHOLOGY REPORTS²³

- Size of tumour
- Status of the margin
- Invasion of lymph vessels
- Extension of the extracutaneous layer
- depth of the tumour
- Lymphocytes that infiltrate tumours
- Pattern of tumour growth
- Further Workup
- Detailed medical history and examination
- Imaging tests (suggested)
- PET/CT scan of the entire body or MRI with contrast
- MRI of the brain, if indicated by clinical evidence
- Biopsy of a sentinel lymph node (the most accurate staging method)
- It is advised to speak with multiple specialists and to carefully handle immunosuppressive medications.

DIAGNOSTIC CRITERIA

1. Tumor-Informed Circulating Tumor DNA (ctDNA) Assay

It has a high sensitivity of 94% in identifying clinically apparent MCC.

If undetectable, the negative ctDNA (surveillance) test has a very high Negative Predictive Value (NPV) of 93% at 135 days, indicating a minimal probability of recurrence during the following three to four months.

The Hazard Ratio (HR) for a positive ctDNA (Surveillance) was 20 [95% CI: 8.3 to 50], indicating a predicted recurrence risk.

Recurrence and ctDNA positive are significantly correlated, even at low levels (<1 MTM/mL).

AUC = 0.86 [95% CI, 0.80 to 0.92] indicates that ctDNA levels over a specific threshold are associated with an increased risk of recurrence.

There is a significant recurrence risk even at low levels of positive ctDNA (17% risk at ctDNA levels <1 MTM/mL)

2. MCPyV (Merkel Cell Polyomavirus) Antibodies detectable in 52% of MCC patients; nonetheless, its sensitivity for the entire MCC patient population is still low.

Although it has a 97% NPV for decreasing antibody titers in patients who are antibody-positive, its low sensitivity restricts widespread use.

3. Imaging-Based Clinical Follow-Up: ctDNA surveillance-based imaging frequencies.

For individuals with low risk of recurrence, a negative ctDNA supports the choice to minimize or postpone imaging. Clinically noticeable recurrence is predicted by positive ctDNA during surveillance, indicating the necessity of more frequent physical examinations and imaging²⁸.

TABLE 2 MCC STAGING^{29, 30}

Stage	Description
Stage I	Tumor confined to skin without regional lymph node metastasis
Stage II	Tumor with regional lymph node involvement
Stage III	Tumor with distant metastasis

TABLE 3 DIAGNOSTIC FACTORS TO BE CONSIDERED IN MCC³¹

Category	Description	Key Points
Lymph Node Ratio (LNR)	Ratio of positive lymph nodes to total lymph nodes dissected	Higher LNR indicates worse outcomes
Immunohistochemical Scoring	:Biomarkers assessed	
	Cytokeratin-20 (CK20) -	Nearly always expressed in MCC
	Neuroendocrine markers (e.g., chromogranin A, - synaptophysin)	Positivity supports diagnosis
Risk-Adjusted Recurrence Tools	Tools estimate recurrence risk based on factors	TNM stage
		Lymph node involvement
		MCPYV status and tumor growth rate

DIFFERENTIAL DIAGNOSIS

MCC shares several characteristics with other small round cell cancers, such as neuroblastoma.

Rhabdomyosarcoma

- Small cell lung cancer

- Lymphomas

Confirmation of Diagnosis

Using markers, immunohistochemistry (IHC) is essential.

CK20 (found in 75–100% of MCC cases)

TTF-1, which is negative in MCC

Neuroendocrine markers, such as synaptophysin and chromogranin³².

MANAGEMENT

A number of clinical, pathological, and patient-specific factors influence the choice of treatment for Merkel Cell Carcinoma (MCC), including:

1. Features of the Tumor

Disease stage:

● Localized: Radiation therapy may be used after surgery, which is frequently the first line of treatment³³.

● Regional: Affects lymph nodes and may call for a mix of systemic therapy, radiation, and surgery³⁴.

● Systemic therapies: such as immunotherapy or chemotherapy are prioritized for distant metastases^{35, 36}.

● Tumor size: To reduce the chance of recurrence, larger tumors may need radiation therapy in addition to surgery

● Location of the tumor: The location of the tumor affects the impact and accessibility of surgery³⁷.

Involvement of Lymph Nodes

To evaluate lymphatic spread, sentinel lymph node biopsy is essential.

Radiation and surgery (lymph node dissection) are usually recommended if lymph nodes test positive.^{40, 41}

3. Factors Specific to the Patient

Comorbidities and general health: Assesses the viability of systemic therapy or surgery.

Age: Patients who are older may not be able to handle intensive therapy or surgery as well⁴².

Performance status: Combination therapy may be appropriate for those who are in better general health.

TABLE 4 STAGING AND SCORING MCC WITH TNM ^{38,39}

CATEGORY	STAGE	DESCRIPTION
T (Tumor Size)	T1	Tumor ≤ 2 cm
	T2	Tumor > 2 cm but ≤ 5 cm
	T3	Tumor > 5 cm
	T4	Tumor invades deep tissues (e.g., bone, muscle, fascia, cartilage)
N (Lymph Node)	N0	No regional lymph node metastasis
	N1a	Micrometastasis
	N1b	Macrometastasis
	N2	In-transit metastasis without lymph node involvement
M (Distant Metastasis)	M0	No distant metastasis
	M1a	Metastasis to distant skin, subcutaneous tissue, or distant lymph nodes
	M1b	Metastasis to lungs
	M1c	Metastasis to other distant sites

4. Molecular and Histological Characteristics

The usage of immune checkpoint inhibitors, such as pembrolizumab or avelumab, may be influenced by PD-L1 expression⁴³.

Status of Merkel cell polyomavirus (MCPyV): linked with prognosis but not directly influencing treatment decision⁴⁴.

5. Recurrence Risk

Adjuvant radiation or systemic therapy may be essential in high-risk instances (such as inadequate excision or positive margins)⁴⁵.

6. Condition of Immunity

Patients with weakened immune systems may benefit less from immunotherapy and have a higher chance of recurrence, necessitating customized strategies.

7. Treatment Availability

Therapy decisions can also be influenced through access to specialized facilities that provide immunotherapy or advanced radiation treatments. [NCCN]

Standard Methods

1. Surgery: To obtain distinct margins for localized MCC, surgery is recommended.
2. Radiation therapy: When surgery is not an option, it is used as a last treatment or as an adjuvant in high-risk instances.
3. Immunotherapy: The first line of treatment for metastatic or incurable MCC is PD-1/PD-L1 inhibitors.
4. Chemotherapy: Originally employed for cases of metastasis, its use has decreased since immunotherapy was developed.

SURGERY

Wide local or Locoregional Excision:

Wide local excision (WLE) is a common surgical approach for treating Merkel cell carcinoma (MCC), involving the removal of the tumor along with 1-2 cm of surrounding healthy tissue. In anatomically delicate areas like the face or hands, achieving wide margins may be impractical, so smaller margins are often paired with adjuvant radiation therapy to address any remaining microscopic disease. Sentinel lymph node biopsy (SLNB) is typically conducted alongside WLE to evaluate regional lymph nodes, aiding in accurate staging and treatment decisions²³.

In the treatment of MCC, recent research compares WLE with Mohs micrographic surgery (MMS). Both surgical approaches are reasonable choices for primary cutaneous MCC, according to a study that was published in the *Journal of the American Academy of Dermatology* and found no discernible difference in mortality outcomes between WLE and MMS. In treating MCC of the head and neck, MMS and WLE had comparable survival outcomes, according to another study published in *JAMA Dermatology*. This suggests that MMS could occasionally be a safe and useful substitute for WLE⁴⁶.

A patient's comorbidities, tumor size, location, and access to specialized surgical skills should all be taken into account when making the decision between WLE and MMS. To optimize patient outcomes in MCC, a multidisciplinary review is necessary to identify the best surgical strategy and whether adjuvant therapies are necessary.

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SLNB) is a key method in managing Merkel cell carcinoma (MCC), giving significant data for staging and therapy planning. The significance of SLNB in identifying subclinical disease spread is shown by research showing that about 26% of MCC patients having the procedure have occult nodal metastases. Furthermore, SLNB has been linked to better overall survival and a lower risk of regional recurrence, underscoring its function in improving patient outcomes⁴⁷. Since it helps with precise staging and guides future treatment choices, the available data

supports the suggestion that SLNB be used for all clinically node-negative MCC patients⁴⁸.

RADIATION THERAPY

The aggressive and uncommon skin cancer known as Merkel cell carcinoma (MCC) is very sensitive to radiation therapy (RT). To improve local and regional control of the disease, RT is commonly used in MCC care, either as a primary treatment or as a supplement to surgery.

Treatment with Adjuvant Radiation: To eradicate any remaining microscopic disease, postoperative radiation therapy is frequently given to the primary tumor site and nearby lymph nodes. Higher survival rates have been linked to this strategy. For example, one study found that patients who had adjuvant radiation therapy had a median survival of 63 months, while those who did not have treatment had a median survival of 45 months^{49,50}.

Final Radiation Treatment: Definitive RT is a substitute for surgery when it is not practical. With doses ranging from 45 to 60 Gy, RT alone can achieve in-field control rates of 80–90% thanks to MCC's special radiosensitivity⁵¹. Radiation therapy in short courses: Short-course RT regimens have been studied recently. Interestingly, a single low dosage of 8 Gy has shown exceptionally good tumor response and control rates, indicating the possibility of less rigorous treatment regimens⁵².

Considerations about in Head and Neck MCC: Because of their close proximity to vital tissues and intricate lymphatic circulation, MCCs in the head and neck region pose particular difficulties. With adjuvant treatment to the initial tumor site and any positive lymph node regions linked to decreased chances of locoregional recurrence, RT is essential in the management of these cases^{14,15}.

PHARMACOLOGICAL THERAPY

IMMUNOTHERAPY

When compared to traditional medicines, PD-1/PD-L1 inhibitors are a far better and safer treatment choice for advanced MCC, greatly improving patient outcomes. In MCC, immune checkpoint inhibitors (ICIs) have the ability to provide long-lasting effects even after treatment ends, suggesting the possibility of long-term remission and providing novel therapeutic approaches that reduce extended therapy exposure⁵³. In MCC, myeloid cells play a role in resistance to PD-1/PD-L1 inhibition. This implies that addressing this immunosuppressive milieu may enhance PD-1 inhibitor effectiveness and even direct combination therapy approaches.

For patients with MCC, extended-duration therapy with shorter dose intervals is a viable and efficient treatment option. By lessening the burden of treatment while maintaining therapeutic advantages, this strategy may enhance quality of life⁵⁴. The success of PD-L1 inhibitors is mostly dependent on neoantigen-specific CD4 T cells, underscoring the significance of T cell responses in

mediating immunotherapy's effectiveness. These results raise the possibility of utilizing these T cells as treatment response indicators⁵⁵. In MCC, TMB and PD-L1 expression are useful indicators of how well a patient will respond to PD-1 medications.

According to the results, molecular profiling can be used to tailor and improve treatment plans, increasing effectiveness and preventing needless therapies for individuals who are less likely to respond⁵⁶. Together, these studies demonstrate that PD-1/PD-L1 inhibitors are a successful treatment for advanced MCC, offering long-lasting effects with tolerable toxicity. However, immunosuppressive myeloid cell-induced therapeutic resistance and patient response variability dependent on molecular markers, such as TMB and PD-L1 expression, have been discovered.

The overall efficacy of immunotherapy in MCC may be improved by combinatorial medicines, tailored treatment regimens based on molecular profiling, and focused strategies addressing immunosuppressive microenvironments.

Avelumab

Dosage: 10 mg/kg administered intravenously every 2 weeks.

Avelumab has shown encouraging improvements in overall survival (OS) and progression-free survival (PFS). Avelumab's promise as a workable alternative for managing metastatic MCC following progression on other medications was highlighted by the persistent responses shown by patients who got it after failing prior treatments. Avelumab's long-term safety and effectiveness, as evidenced by its 33.7% overall response rate (ORR) and sustained responses in a subgroup of patients. According to the study, Avelumab is a significant first-line therapeutic option for advanced MCC because it is linked to long-lasting tumor control when used consistently in this context. Advanced MCC can be effectively treated with avelumab. Avelumab's overall effectiveness in advanced stages of MCC was supported by the review of data from clinical trials and real-world evidence. It noted an impressive overall response rate, particularly in patients with PD-L1-positive tumors, and favorable safety outcomes with manageable side effects⁵⁷. Reaffirmed the contribution of Avelumab to a longer survival time, even in patients with difficult metastatic MCC. The findings of clinical trials were in line with the real-world survival data, which showed encouraging overall survival and response rates, especially in patients with improved immunological profile⁵⁸.

Patients with metastatic MCC who achieved a complete response (CR) after a year of Avelumab treatment could safely discontinue therapy, with persistent benefits shown in those with a verified CR via PET/CT. Avelumab demonstrated a notable reduction in tumor burden and improved survival outcomes, with long-lasting benefits even in patients with prior treatments⁵⁹. Combining Avelumab and radiation therapy showed positive clinical results in patients with no improvement from treatment, suggesting radiation may help overcome

immunological resistance. Long-term follow-up of avelumab in metastatic MCC patients continued to show survival benefits, with a manageable safety profile and sustained remission in a significant number of patients⁶⁰.

Pembrolizumab

Dose: 200 mg intravenously every 3 weeks or 400 mg every 6 weeks.

The evidence for pembrolizumab as a first-line treatment for recurrent or metastatic MCC is further strengthened by the KEYNOTE-913 research. High response rates, long-lasting survival advantages, and controllable toxicity indicate that pembrolizumab ought to be regarded as a first-line treatment for this aggressive cancer, especially in patients who test positive for PD-L1. With this immunotherapy option, patients can expect a longer, more permanent disease-free survival with controllable side effects, which is a significant improvement over standard chemotherapy. Particularly for patients with advanced-stage Merkel cell carcinoma, pembrolizumab offers a promising new therapeutic avenue with the added advantages of substantial tumor control and prolonged survival.

Nivolumab

Dosage: 240 mg administered intravenously every 2 weeks

For patients with resected MCC, nivolumab is an effective adjuvant treatment that can increase disease-free survival and possibly lower the chance of relapse following surgery⁶¹. When used as an adjuvant therapy, nivolumab improves disease-free life in MCC that has been entirely removed, offering a promising means of preventing relapse and boosting long-term survival following surgery⁶². For patients with fully resected MCC, nivolumab provides substantial advantages in adjuvant settings, mainly through enhancing disease-free survival and lowering the chance of recurrence. One crucial post-operative therapeutic option for MCC patients, especially those with a high risk of recurrence, is nivolumab.

COMBINATION THERAPY

Bevacizumab combined with atezolizumab

Atezolizumab: 1,200 mg intravenously (IV) every 3 weeks.

Bevacizumab: 15 mg/kg IV every 3 weeks.

For patients with advanced Merkel Cell Carcinoma, the combination of bevacizumab and atezolizumab presents a viable therapeutic option. In comparison to previous treatment outcomes, it showed higher efficacy in terms of response rates, PFS, and OS. In the majority of patients, it also offered manageable safety. For MCC, this combination therapy may be a useful approach, particularly when other treatments have not worked or are not practical⁶³.

Nivolumab combined with Ipilimumab

Nivolumab (OPDIVO): 1 - 3mg/kg administered

intravenously every 3 weeks.

Ipilimumab (Yervoy): 1 - 3 mg/kg administered intravenously every 3 weeks.

Combining Ipilimumab and Nivolumab offers patients with anti-PD-L1/PD-1 refractory MCC a potentially successful treatment option, demonstrating that resistance to early immunotherapy can be overcome by dual immune checkpoint inhibition. These results highlight the wider significance of using combination therapy to handle resistant MCC patients, even though they are not explicitly focused on atezolizumab and bevacizumab⁶⁴.

CHEMOTHERAPY

Chemotherapy In addition to highlighting the fact that over one-third of patients either had stable disease or did not respond to treatment, chemotherapy can be somewhat helpful in managing disease. The longevity of the treatment varied among those who responded to chemotherapy, although most had relapsed by months. In particular, the very short median duration of response highlighted the limited long-term benefits of chemotherapy for metastatic MCC. Chemotherapy did not improve long-term survival, even though it produced immediate responses. Those with metastatic disease continued to have a poor prognosis, especially after the response to chemotherapy had diminished.

Although some patients with metastatic MCC may have short-term advantages with chemotherapy, its overall response rates and durability are low. These results confirmed that immune checkpoint inhibitors and other therapeutic alternatives are more effective in treating this aggressive kind of skin cancer⁶⁵. Retifanlimab, anti-LAG-3, and anti-TIM-3 are three immunotherapy medications being studied in the TRICK-MCC trial for patients with metastatic Merkel cell carcinoma (MCC) that has progressed following conventional immunotherapy. Finding out if this combination can improve the immune system's ability to recognize and eliminate cancer cells is the aim. The FDA has approved Retifanlimab for MCC, while the other two medications are still in the experimental stage. The Fred Hutchinson Cancer Centre and the University of Washington in Seattle are hosting the trial.

Although the research medications are given away for free, participants may have to pay for their medical care. Participants are free to leave the experiment at any moment, and it is entirely voluntary⁶⁶.

CHALLENGES IN MCC

Challenges in Prognosis:

MCC has a significant death rate, frequently higher than that of melanoma. Male sex, severe illness stages, and elderly age are associated with worse results, and the 5-year survival rate varies from 30% to 64%.

Challenges in Diagnosis:

Because MCC grows quickly and its early symptoms are mild, it can be challenging to detect early. On sun-exposed skin areas, it frequently manifests as a firm,

painless nodule that grows quickly. Delays in diagnosis are caused in part by the disease's rarity and the absence of distinct early symptoms. Therapy Difficulties: MCC can be treated with immunotherapy, radiation, and surgery. But the prognosis is still bad, thus early diagnosis and efficient treatment plans are required.

Challenges in Resistance to Standard Treatments:

1. Although immunotherapies such as anti-PD-1/PD-L1 drugs (e.g., avelumab or pembrolizumab) are helpful in certain cases of MCC, a small percentage of patients do not react to treatment, or the cancer continues to advance in spite of it. For individuals whose cancer no longer responds to these drugs, there are no FDA-approved treatments⁶⁷.

2. **Aggressive Disease Progression:** MCC frequently advances quickly before an effective treatment can be started since it is extremely aggressive and prone to metastasis. This reduces the efficacy of conventional treatments like chemotherapy, which typically only offer temporary respite with no long-term advantages for survival⁶⁸.

3. **Toxins Associated with Treatment:** Both current treatments and the more recent experimental immunotherapy combinations have the potential to have serious adverse effects, such as immune-mediated harm to potentially fatal organs including the kidneys, liver, or lungs. This makes it difficult to manage and choose which patients to treat⁶⁹.

CONCLUSION

Merkel Cell Carcinoma (MCC) remains a formidable clinical challenge due to its rapid progression, aggressive behavior, and frequent diagnostic delays. Significant strides have been made in its management, particularly through immune checkpoint inhibitors like avelumab, pembrolizumab, and nivolumab, which have revolutionized treatment by providing durable responses and improving survival. Emerging combination therapies and experimental agents hold promise for addressing cases resistant to standard treatments.

Early and accurate diagnosis is pivotal in improving patient outcomes, necessitating advanced techniques like sentinel lymph node biopsy and ctDNA monitoring. Furthermore, understanding the molecular and genetic underpinnings of MCC is essential for the development of targeted therapies and personalized treatment strategies

Future research should focus on optimizing diagnostic accuracy, identifying biomarkers for better patient stratification, and refining immunotherapy combinations to overcome resistance. Additionally, strategies to mitigate immunotherapy-associated toxicities and improve accessibility in low-resource settings will be key in managing this rare but aggressive malignancy effectively. Only through continued innovation and collaborative research can the survival and quality of life for MCC patients be significantly enhanced.

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