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Review

Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs

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Abstract Merkel cell carcinoma (MCC) is a rare skin cancer that is associated with Merkel cell polyomavirus infection in most cases. Incidence rates of MCC have increased in past decades. Risk factors for MCC include ultraviolet light exposure, immunosuppression and advanced age. MCC is an aggressive malignancy with frequent recurrences and a high mortality rate, although patient outcomes are generally more favourable if the patient is referred for treatment at an early stage. Although advances have been made recently in the MCC field, large gaps remain with regard to definitive biomarkers and prognostic indicators. Although MCC is chemosensitive, responses in advanced stages are mostly of short duration, and the associated clinical benefit on overall survival is unclear. Recent nonrandomised phase 2 clinical trials with anti–PD-L1/PD-1 antibodies have demonstrated safety and efficacy; however,

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there are still no approved treatments for patients with metastatic MCC. Patients with advanced disease are encouraged to participate in clinical trials for treatment, indicating the largely unmet need for durable, safe treatment within this population.

1. Introduction

Merkel cell carcinoma (MCC) is a rare neuroendocrine, cutaneous malignancy that was first described in 1972 [1,2]. MCC is highly aggressive, and more than one-third of patients die of MCC, making it twice as lethal as malignant melanoma [2,3]. Up to 37% of patients present with nodal disease, and 6–12% of patients present with distant disease [4–9]. The at-risk population includes the elderly, and people with immunosuppression from organ transplant and HIV infection [10–13]. A current, past or concurrent diagnosis of chronic lymphocytic leukaemia (CLL) and other haematologic malignancies is more frequent in patients with MCC [14,15]. MCC tumourigenesis is linked to the presence of clonally integrated Merkel cell polyomavirus (MCPyV) and/or mutagenesis from ultraviolet (UV) light exposure [16–18].

The incidence rate of MCC is variable across different regions of the world. The Surveillance of Rare Cancers in Europe (RARECARE) database reported an incidence rate of 0.13 per 100,000 between 1995 and 2002 [19]. In the United States of America (USA), the incidence rate reported in the most recent analysis of Surveillance, Epidemiology, and End Results (SEER) data from 2011 was 0.79 per 100,000 [7]. The frequency of MCC is highest in Australia, where the age-adjusted incidence rate reported in Queensland was 1.6 per 100,000 from 1993 to 2010 [20]. The estimated mortality rate for MCC is between 33% and 46% [7,21,22]. The incidence and disease-specific mortality rates within USA have significantly increased since 1986 [7]. In recent years, there have been major advancements in our understanding of MCC biology; however, survival rates remain low (5-year overall survival [OS] 0–18%) for advanced-stage MCC [22,23]. There are currently no approved therapies for advanced-stage MCC, and the choice of treatment depends on the location of the tumour and comorbidities, highlighting the acute unmet need for effective treatment options with a good safety and tolerability profile [24,25].

2. Methods

Literature searches of PubMed were conducted in April 2015 and January 2016 for reports published in English since database inception using the search terms 'Merkel cell carcinoma', combined with 'pathophysiology', 'stage', 'symptom', 'diagnosis', 'metastasis', 'prognosis', 'burden', 'prevalence', 'incidence', 'morbidity', 'mortality', 'survival', 'risk factor', 'Merkel cell polyomavirus', 'UV', 'guidelines', 'treatment', 'chemotherapy' and 'radiotherapy'. Publications since January 2016 were also selectively included. ClinicalTrials.gov was used to identify ongoing clinical trials being conducted in advanced MCC. In addition, we searched congress abstracts from 2010 through June 2016 using the term 'Merkel cell carcinoma'. Most clinical publications were case series and case reports on small patient populations and retrospective analyses based on institutional or national databases.

3. Clinical burden

3.1. Clinicopathological features

MCC presents as a firm, painless, rapidly enlarging, red–violet cutaneous tumour nodule that is typically dome-shaped [4,26]. MCC nodules are more frequently located in sun-exposed areas of the head and neck or upper extremities [4,26–28]. Heath *et al.* developed the AEIOU acronym to define the clinical features associated with MCC: asymptomatic/lack of tenderness, expanding rapidly, immune suppression, older than age 50 and UV-exposed site on a person with fair skin. In a study of 195 patients, 89% presented with three or more of the AEIOU characteristics [4].

Three histological subtypes have been identified—trabecular, intermediate and small cell—although the utility of these subtype classifications is currently unclear [29–31]. The trabecular type, which is the most differentiated, is rare and usually only seen in mixed tumours. The intermediate type is characterised by basophilic nuclei with high mitotic activity and is most common. The small-cell type is undifferentiated and indistinguishable from small cell carcinomas of other anatomical sites, e.g. lung. Histopathological characteristics of MCC include hyperchromatic nuclei and high mitotic activity [30,32]. Immunohistochemistry is characterised by positive staining for cytokeratin 20 and neuron-specific enolase and negative staining for thyroid transcription factor-1 [33,34].