Merkel cell carcinoma and immune checkpoint inhibition: where do we stand now?

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Immune checkpoint inhibition (ICI) has been acknowledged as a breakthrough treatment in multiple advanced cancer types. This is also the case in metastatic Merkel Cell Carcinoma (MCC), a disease that is historically associated with a poor prognosis. Recently, several randomized trials demonstrated superior results of ICI compared to chemotherapeutic agents in patients with metastatic MCC, with less toxicity, an increased overall survival (OS), and more durable responses. Therefore, ICI is now generally considered as a new standardtreatment option in this setting.

INTRODUCTION

MCC is a rare, aggressive, neuro-endocrine tumor of the skin. Locoregional recurrence and metastasis of the disease are frequent and the associated mortality rate is high, with a five-year overall survival of 55.6%.[1] The pathophysiology of MCCs is mainly based on UV-exposure, impaired immune function, older age and Merkel cell polyoma virus DNA integration (MCPyV).[2] The current standard treatment for MCC mainly depends on the tumor stage. In patients with localized disease, the standard treatment primarily consists of surgery and/or radiotherapy. On the other hand, chemotherapeutics are mostly reserved for patients with metastatic disease. In general, MCC is considered to be a chemo-sensitive tumor type. However, due to their rarity, literature data regarding chemotherapy schedules in metastatic MCC are scanty.[1] Currently, patients with metastatic disease are preferably treated with a combination of platinum agents and etoposide. Unfortunately, the responses to these platinum doublets are not durable and patients usually relapse within 8 months. Moreover, patients also suffer from multiple chemotherapy-associated side effects or comorbidities. As such, the need for alternative treatments is acute. Novel therapeutic agents such as anti-angiogenic and anti-apoptotic proteins, PARP (poly-ADP ribose polymerase)-inhibitors, tyrosine kinase inhibitors, mTOR inhibitors and many others are still under investigation in several clinical trials.[3] Recently, many successes have been achieved with ICI in several cancer types. MCC remains a rare type of cancer but recent understanding of the disease biology suggested immune susceptibility, making the disease a possible target for ICI. To further decipher its biological mechanisms and analyze the efficiency of these novel therapies, several international, multicenter, novel design and cooperative group trials have been conducted.[4] In this short clinical review, we will discuss the most recent activity and safety data with anti-PD-(L)1 (avelumab, pembrolizumab and nivolumab) and anti-CTLA4 (ipilimumab) agents in MCC.[3]

MERKEL CELL POLYOMA VIRUS DNA INTEGRATION

As previously mentioned, MCPyV DNA integration in the Merkel cell genome is one of the risk factors for tumor development. Overall, 80% of MCCs are MCPyV-positive and this positivity is associated with a better prognosis than MCPyV-negative MCC.[5] Infection with MCPyV is ubiquitous, usually occurs during

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childhood, and has also been detected in healthy human skin cells.[2] MCPyV-positive MCC express large T-antigen (LTa) in the nuclei of nearly every MCC-cell, which inactivates p53 and Rb. In turn, these viral oncoproteins induce high serum LTa-antibodies (which are correlated to tumor burden), and CD4+-and CD8+ T-cell activation. Upon chronic exposure to these viral oncoproteins, the expression of inhibitory receptors such as PD-1 may be upregulated. This implies that virus infection is not only correlated to MCC tumorogenesis, but may also enhance immune evasion through different mechanisms.[6] Like in other virus-induced cancers, immune dysfunction is considered as an important risk factor for tumor promotion and development and it is associated with a worse prognosis.[2] In MCC this phenomenon was confirmed with immunodeprived patients (HIV-infection, organs transplantation, lymphoid malignancies…) being at a higher risk of MCC development, with worse outcomes. On the other hand, increased lymphocyte infiltration of the tumor on histological samples or cessation of immunosuppression was associated with spontaneous MCC regression.[6]

MCPyV-negative MCC is another disease strain that is characterized by increased genomic instability and a high mutational load (probably due to high UV-exposure), resulting in a high burden of neoantigens. Although multiple studies note a humoral and cellular adaptive immune response against it, MCC is still able to escape the immune response, implying that immune tolerance takes place.[2] Notably, over 56% to 81% of MCPyV-positive MCC express PD-L1 on tumor cells (with a cut-off by 5% of positive tumors), while MCPyV-negative MCC are predominantly negative for PD-L1 expression.[7,8]

ICI FOR ADVANCED MCC

Avelumab is a humanized IgG1 antibody directed against PD-L1 and is the first ICI agent that was approved as first-line treatment for advanced, metastatic MCC-patients in Europe, the United States and Japan. These approval is based on the results of the Javelin Merkel 200 trial.[9,10] This is a phase 2, prospective, open-label, single-arm trial in advanced or metastatic MCC. Patients received avelumab on a two-weekly basis at 10mg/kg.[10] In part A, 88 patients with chemotherapy refractory metastatic MCC were treated with avelumab. An overall response rate (ORR) of 33.0% and responses were also shown to be durable, with 74% of responses persisting for at least 1 year. The median overall survival (OS) in this study was 12.9 months, with a one year progression-free survival (PFS) rate of 30%. In comparison, the historical PFS rate with second-line chemotherapy (mostly cisplatin-based) in this setting is 0%. The treatment duration ranged from 1 to 14 months.[11] In part B, 39 patients received avelumab in first line. In this setting the efficacy of avelumab was even more promising with a confirmed ORR of 62.1% and a median PFS of 9.1 months. The median duration of treatment was 12 weeks (range: 2.0-49.9 weeks).[9] The safety profile of avelumab was generally manageable and tolerable. In part A of the trial, 10.1% of patients dropped out of the study due to immune-related adverse events (irAEs).[11] In part B, 71.8% of evaluable patients reported irAEs, but there were no reported cases of grade 4 irAEs or treatment-related deaths.[9]

In a phase II, multicenter non-controlled study, 50 patients with advanced MCC (stage IIIB and stage IV) received first line treatment 2mg/kg of pembrolizumab (an IgG4 anti-PD-1 antibody) every three weeks for a maximum period of two years or until the patient encountered disease progression, unacceptable toxic events or a complete response. Among the 42 patients with at least 21weeks of follow-up, the ORR was reported to be 50%. The OS rate at 18 months was 68%. In 94% of patients, an irAE of any grade was encountered: 30% experienced an irAE with grade 3 or higher, including one treatment related death. These results are based on the longest follow up of MCC-patients with advanced disease treated with pembrolizumab as a first-line therapy.[1]

Nivolumab is another monoclonal anti-PD-1 antibody that has been investigated in advanced MCC. In the checkmate 358 phase II trial, 22 treatment-naïve (N= 14) and treatment-experienced (N=8) patients with advanced MCC were treated with nivolumab 240mg two-weekly until progressive disease or unacceptable toxicity. An ORR of 63% and 71% was noted in treatment-naïve and treatment experienced patients, respectively. Regarding the incidence of irAE: 68% of patients encountered an irAE of any grade, while grade 3/4 irAE occurred in 20% of patients. Four patients had to discontinue the treatment for reasons of toxicity.[13]

Additionally, nivolumab was evaluated in the neo-adjuvant setting. In this study, 22 patients with resectable MCC received two times 240mg of nivolumab every 14

days, followed by surgery two weeks after the last nivolumab administration. Radiologic evaluation was performed before surgery in 20 patients and revealed tumor regression (13-100% reduction) in 16 cases. In the surgical specimens (<10% viable tumor cells) of 17 patients, pathological regression was shown in 11 patients, with a complete response in 8 patients. Twenty-one patients were eventually followed after surgery and all were progression-free at six months, while only two patients relapsed after 12 months. irAEs occurred in 36% of patients and 4% encountered grade 3/4 irAEs.[14] All objective responses occurred independent of PD-L1 expression and MCPyV-status.

In both the investigated settings, nivolumab was considered a beneficial treatment with durable effects and a manageable safety profile in local and metastasized MCC.

The efficacy of Ipilimumab (an anti-CTLA4 antibody) monotherapy has only been described as a case-report of five patients with recurrent, metastatic MCC. Altogether, results were in favor of ipilimumab. Although no OS results were reported, the median PFS by Kaplan-Meier was approximately 12 months (0.0; 27.3).[15]

CONCLUSIONS

Recently ICI has been acknowledged as a breakthrough treatment in multiple advanced cancer types. This is also the case in metastatic MCC, a disease that is associated with a poor prognosis. ICI can now be considered a new treatment option given the superior results compared to chemotherapeutic agents, with less toxicity, increased overall survival, and more durable responses. Avelumab was the first FDA approved ICI for treatment of MCC, with spectacular results in patients with advanced disease. Other anti-PD-(L)1 antibodies are still under investigation in multiple phase II clinical trials but are showing promising results.

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