Irish Medical Journal
Established 1867

Issue: Ir Med J; Vol 114; No. 2; P280

Advanced Merkel Cell Carcinoma in the Era of Immunotherapy

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Abstract

Introduction

Recent advances in our understanding of tumour immunology has led to new treatment options for patients with advanced Merkel cell carcinoma, a rare malignant skin cancer with a poor prognosis.

Cases

Case 1 – a 77-year-old man with pancreatic metastases from a Merkel cell carcinoma primary achieved a complete response with second line avelumab maintained for at least 36 months.
Case 2 – a 58-year-old man with metastatic Merkel cell carcinoma involving liver achieved a complete response with second line pembrolizumab sustained for at least 48 months.
Case 3 – a 57-year-old woman with extensive nodal metastases from a Merkel cell carcinoma primary did not respond to second line pembrolizumab and died.

Outcome

Three patients under our care with advanced Merkel cell carcinoma were treated with immunotherapy following traditional chemotherapy. Two patients with distant metastases to the pancreas and liver respectively achieved a sustained complete response of at least 36 months. One patient did not respond and died.

Conclusion

The treatment paradigm for advanced Merkel cell carcinoma has shifted dramatically with the advent of immunotherapy, the new standard of care in metastatic disease. These cases illustrate the dramatic responses that are possible but also underline the need for further research.

Introduction

Merkel-cell carcinoma (MCC) is a rare cutaneous malignancy arising from epidermal mechanoreceptors with an incidence of approximately 1 in 100,000, rising exponentially with age.[1] The majority of lesions arise on the head, neck or upper limb and may be misdiagnosed as a sebaceous cyst or lipoma. Rapidly growing, red-blue, fleshy lesions on sun-exposed skin (Figure 1), particularly in the elderly and/or immunosuppressed, should raise suspicion for MCC.[1] Whilst most cases are localized at diagnosis (65%), a minority present with distant disease (8%), conferring a poor prognosis with a 5-year overall survival of just 14%.[2]

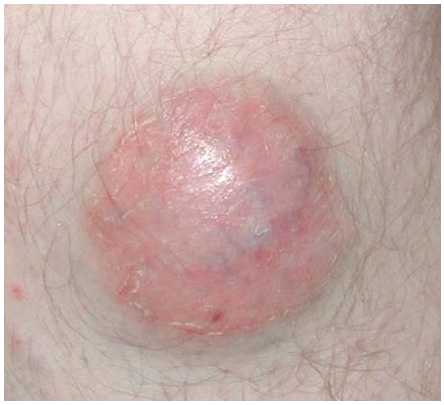

Figure 1. Merkel cell carcinoma (reproduced with permission from merkelcell.org)

The pathogenesis of MCC is associated with a double-stranded DNA polyoma virus (MCPyV) which can be isolated in about 80% of cases.[3] Although a constituent of the human skin microbiome, MCPyV can be incorporated into the tumour genome leading to the expression of several oncoproteins.[4,5] Elevated antibody titres to these oncoproteins may correlate with risk of recurrence and influence the intensity of surveillance.[6] In Ireland, testing for polyoma virus and antibodies is not routine. In viral-negative disease, ultraviolet radiation plays a prominent role in carcinogenesis leading to a high mutational burden. This is supported by several observations including the propensity of MCC to occur on sun exposed skin[1] and the correlation between regional incidence rates and UV solar index, with Australia possessing the highest rates worldwide.[7] Patients who are immunosuppressed due to B cell malignancies, organ transplantation or HIV infection are much more likely to be diagnosed with MCC.[8,9] Immunosuppression may facilitate greater replication of the polyoma virus and increase the likelihood of incorporation into the genome.

MCC is an aggressive cutaneous neuroendocrine tumour on the same histological spectrum as small cell lung cancer or high-grade neuroendocrine carcinomas and up until recently the preferred initial treatment option was chemotherapy with a combination of carboplatin and etoposide. Despite this approach outcomes in advanced disease are poor with a median progression-free survival of just 3 months and overall survival between 6-10 months.[10] However, the treatment paradigm has shifted radically in recent years with the emergence of immune checkpoint inhibitors, which have already proven effective in metastatic melanoma and cutaneous squamous cell carcinoma.[11,12]

The immune checkpoint refers to the receptor-ligand interaction between T lymphocytes and host cells that prevents autoimmunity. One such interaction involves the Programmed Death (PD) receptor on T cells and associated ligand (PDL1) expressed on host cells. Tumour cells can upregulate expression of PDL1 thereby suppressing immune-mediated destruction, but this camouflage can be lifted by inhibitors such as pembrolizumab, avelumab, and nivolumab. Herein we report our early experience in the treatment of advanced MCC with immunotherapy.

Case 1

A 77-year-old man presented with a painless lesion on his left upper lip. His past medical history included hypertension and smoking. There was no history of immunosuppression or autoimmunity, but he had significant sun-exposure having spent several months each year living in Spain. Excision biopsy was performed confirming a Stage I MCC (less than 2cm in maximum diameter). This was followed by adjuvant radiotherapy and workup did not reveal any evidence of local or distant metastases. Eight months later he represented with left sided cervical lymphadenopathy and a neck dissection was undertaken revealing a single 2.8cm deposit of MCC. Adjuvant radiotherapy was delivered. A year later surveillance imaging demonstrated a 5cm x 10cm mass in the pancreatic neck (Figure 2) with endoscopic ultrasound fine needle aspirate confirming a metastatic MCC deposit. There was associated retroperitoneal lymphadenopathy and low volume lung metastases. He underwent chemotherapy and although he could only complete two cycles of carboplatin-etoposide due to Grade 4 fatigue, he achieved an excellent partial response. Based on a compassionate access programme, an anti-PDL1 antibody, avelumab (Bavencio™), was commenced for metastatic MCC. Of note the MCPyV status was not known. Within 3 months there was a complete radiological response (Figure 3) which has been maintained for at least 36 months with minimal adverse effects.

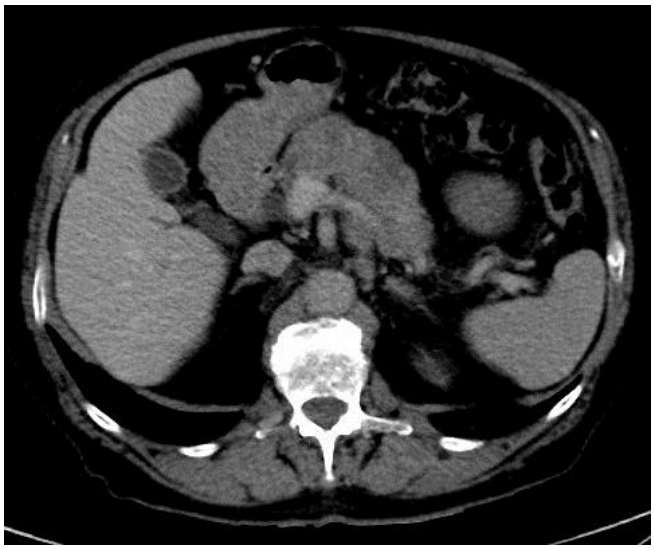

Figure 2. Pre-treatment axial CT-abdomen demonstrating the pancreatic mass.

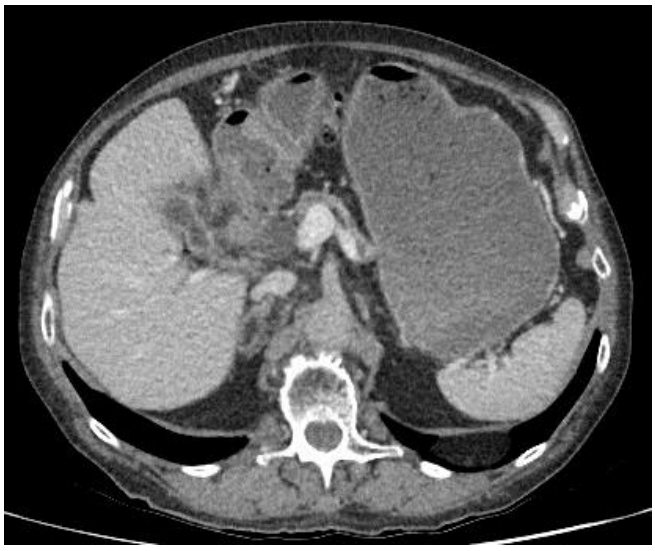

Figure 3. Complete response after 3 months of avelumab.

Case 2

A 58-year-old man with a background of psoriasis managed with an immunosuppressant biological agent, adalimumab, presented to his General Practitioner with a painless swelling on the dorsum of his left hand, growing over the preceding 3 months. The lesion was clinically diagnosed as a sebaceous cyst, but subsequent excision was difficult and therefore the patient was referred to a plastic surgeon for full excision. Immunohistochemical staining for synaptophysin, chromogranin and CK20 was positive confirming MCC. Imaging revealed pathological left-sided axillary lymphadenopathy and multiple liver metastases, biopsy of the latter confirmed Stage IV disease. Initial systemic treatment consisted of four cycles of chemotherapy with carboplatin and etoposide which induced a partial response. Based on emerging data supporting the role of immunotherapy in the metastatic setting, funding from the hospital was approved for the anti-PD1 antibody pembrolizumab (Keytruda^{TM}). Remarkably, the patient achieved a complete clinical and radiological response and completed 2 years of immunotherapy with no Grade 3 or 4 adverse events. Currently the patient remains off treatment with no measurable disease representing overall survival of at least 48 months.

Case 3

A 57-year-old woman with hypertension and monoclonal gammopathy of uncertain significance presented with painless left-sided groin swelling which had developed over a few months. Core biopsy of an inguinal lymph node established the diagnosis of advanced MCC. Staging with PET-CT confirmed Stage III disease with no distant metastases. Initially she received two cycles of carboplatin-etoposide with a partial response but within 1 month the adenopathy rapidly progressed requiring salvage radiotherapy. Subsequently pembrolizumab was commenced via a compassionate access programme, but further adenopathy developed in the retroperitoneum and left axilla therefore it was discontinued after 7 cycles. She underwent experimental electrochemotherapy in combination with pembrolizumab but there was no significant benefit. The patient died from progressive disease 18 months after the original diagnosis.

Discussion

This report describes our early experience treating advanced MCC, the management of which has been revolutionised in the last decade by the emergence of immunotherapy. The rationale for targeting the immune system in MCC is based on observations regarding its immunogenicity, namely its association with immunosuppression, UV radiation leading to mutational burden and the MCPyV.[1,3,5] Recent evidence suggests that a third of cases demonstrate a high mutational burden, a genetic state characterised by greater expression of neoantigens, thus providing more signals for an immune response.[13] However, although tumour mutational burden (TMB) and MPcyV status as well as PD-L1 expression have been shown to be associated with increased response rates, these have not been validated as predictive biomarkers and therefore were not assessed in our patients.

Randomised controlled trials are difficult to undertake in this disease given its rarity, but emerging data, albeit phase I/II trials, has shown significant durable activity in metastatic disease.

Immunotherapy with checkpoint inhibitors has recently been recommended as the standard of care in the US in the first line setting for advanced disease.[14]

Part A of the JAVELIN Merkel 200 study investigated avelumab in patients with metastatic MCC previously treated with chemotherapy.[15] In an exploratory analysis after 3 years of follow up the objective response rate was 33%, the median duration of response was 40.5 months and the 3 year survival rate was 32%. This resulted in FDA approval, the first in this context. In Part B of this trial patients who were treatment naïve received avelumab and an interim analysis has demonstrated a higher response rate of 62% and a median PFS of 9.1 months.[16] Our patient treated with avelumab had a complete and sustained response, which is even more remarkable because pancreatic metastases from MCC are typically fatal within 3-9 months.[17]

In the KEYNOTE-017 study, pembrolizumab was shown to produce a 56% response rate in chemotherapy naive patients with Stage IV MCC, independent of tumour PDL1 expression and MCPyV status.[18] The same study demonstrated an overall survival at 3 years of 64%, almost three times better than historical data with chemotherapy. Of the two patients we treated with pembrolizumab, one had a complete response and remains alive with no identifiable disease, whilst another had progression of disease and died. Although this is a small cohort of patients these vastly different outcomes reflect our incomplete understanding of tumour immunology in this aggressive disease.

There are also data to support the use of nivolumab in metastatic MCC. In the Checkmate 358 phase I/II trial, reported in abstract form, the response rates in treatment naïve patient were up to 73%.[19]

Initially, all three cases were treated in a conventional manner involving platinum-based chemotherapy before immunotherapy was commenced. It is possible that the two patients who achieved a significant response to chemotherapy could have experienced a sustained disease-free survival without the need for additional immunotherapy. However, this was considered highly unlikely as historically the median duration of complete response is just 6 months in metastatic disease.[10] Although chemotherapy is associated with a high response rate it is typically short-lived with median progression free survival of just 3 months.[10] Therefore the rationale to increase the likelihood of a durable response with the sequential addition of immunotherapy was strong and highly successful in two of the three cases achieving an overall survival of over 3 years.

Immune related adverse events have been well documented with immune checkpoint inhibitors, in particular in patients with pre-existing autoimmune conditions. None of our patients experienced any grade 3 or 4 adverse events from immunotherapy. One patient with psoriasis did notice increased activity of disease but this was managed effectively with topical treatment.

The correlation between immune-related toxicity and efficacy in metastatic melanoma has been reported with combination therapy, but there is no data to support this in metastatic MCC.[20] In the JAVELIN Merkel 200 study and the largest expanded access program (EAP) series the most common treatment related adverse effects of avelumab were infusion reaction, fatigue and rash, the majority of which were grade II or less. However, the main toxicity of immunotherapy may prove to be financial.

Funding for immunotherapy in rare diseases such as MCC historically depended on philanthropy and compassionate access programmes. However, in 2019, avelumab was approved for reimbursement by the National Centre for Pharmacoeconomics (NCPE) for use in metastatic MCC after prior chemotherapy. Meanwhile, the FDA has approved avelumab in all settings for the treatment of metastatic MCC. The American National Comprehensive Cancer Network (NCCN) has recommended avelumab, pembrolizumab and nivolumab for the treatment of metastatic MCC and discouraged the use of systemic chemotherapy, unless there is a contraindication to immunotherapy or progression of disease after previous treatment with immunotherapy.[14]

Similarly to malignant melanoma, the potential of immunotherapy in the neoadjuvant and adjuvant management of MCC is also an exciting prospect. Recently, a phase I/II study demonstrated that just two doses of neoadjuvant nivolumab produced a pathological complete response in almost 50% of patients with resectable stage II-IV, regardless of PDL1, TMB and MCPyV status.[22] Clinical trials are ongoing to further evaluate these strategies but in the meantime there is sufficient evidence to recommend immunotherapy as a first line treatment in metastatic disease, offering hope to patients with an otherwise poor prognosis.

Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare.

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References:

1. Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Penas PF, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol. 2008;58(3):375-81.
2. Harms KL, Healy MA, Nghiem P, Sober AJ, Johnson TM, Bichakjian CK, et al. Analysis of Prognostic Factors from 9387 Merkel Cell Carcinoma Cases Forms the Basis for the New 8th Edition AJCC Staging System. Ann Surg Oncol. 2016;23(11):3564-71.
3. Santos-Juanes J, Fernandez-Vega I, Fuentes N, Galache C, Coto-Segura P, Vivanco B, et al. Merkel cell carcinoma and Merkel cell polyomavirus: a systematic review and meta-analysis. Br J Dermatol. 2015;173(1):42-9.
4. Sastre-Garau X, Peter M, Avril MF, Laude H, Couturier J, Rozenberg F, et al. Merkel cell carcinoma of the skin: pathological and molecular evidence for a causative role of MCV in oncogenesis. J Pathol. 2009;218(1):48-56.
5. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science. 2008 Feb 22;319(5866):1096-100. doi: 10.1126/science.1152586. Epub 2008 Jan 17.

6. Paulson KG, Lewis CW, Redman MW, Simonson WT, Lisberg A, Ritter D, et al. Viral oncoprotein antibodies as a marker for recurrence of Merkel cell carcinoma: A prospective validation study. Cancer. 2017;123(8):1464-74.
7. Girschik J, Thorn K, Beer TW, Heenan PJ, Fritschi L. Merkel cell carcinoma in Western Australia: a population-based study of incidence and survival. Br J Dermatol. 2011;165(5):1051-7.
8. Howard RA, Dores GM, Curtis RE, Anderson WF, Travis LB. Merkel cell carcinoma and multiple primary cancers. Cancer Epidemiol Biomarkers Prev. 2006;15(8):1545-9.
9. Clarke CA, Robbins HA, Tatalovich Z, Lynch CF, Pawlish KS, Finch JL, et al. Risk of merkel cell carcinoma after solid organ transplantation. J Natl Cancer Inst. 2015;107(2).
10. Iyer JG, Blom A, Doumani R, Lewis C, Tarabadkar ES, Anderson A, et al. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma. Cancer Med. 2016;5(9):2294-301.
11. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019;20(9):1239-51.
12. Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. N Engl J Med. 2018;379(4):341-51.
13. Knepper TC, Montesion M, Russell JS, Sokol ES, Frampton GM, Miller VA, et al. The Genomic Landscape of Merkel Cell Carcinoma and Clinicogenomic Biomarkers of Response to Immune Checkpoint Inhibitor Therapy. Clin Cancer Res. 2019;25(19):5961-71.
14. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology, most recent update, 2020. [Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.]
15. Kaufman HL, Russell JS, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after >/=1 year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial. J Immunother Cancer. 2018;6(1):7.
16. D'Angelo SP, Russell J, Lebbe C, Chmielowski B, Gambichler T, Grob JJ, et al. Efficacy and Safety of First-line Avelumab Treatment in Patients With Stage IV Metastatic Merkel Cell Carcinoma: A Preplanned Interim Analysis of a Clinical Trial. JAMA Oncol. 2018;4(9):e180077.
17. Ghouri YA, Krishna SG, Kundu UR, Bhutani MS, Lee JH, Ross WA. A case series and literature review of Merkel cell carcinoma metastasizing to pancreas. Dig Dis Sci. 2015;60(6):1805-12.
18. Nghiem P, Bhatia S, Lipson EJ, Sharfman WH, Kudchadkar RR, Brohl AS, et al. Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy. J Clin Oncol. 2019;37(9):693-702.
19. Topalian SL, Bhatia S, Hollebecque A, Awada A, Boer JPD, Kudchadkar RR, Goncalves A, Delord J-P, Martens UM, Picazo JML, et al: Abstract CT074: non-comparative, open-label, multiple cohort, phase 1/2 study to evaluate nivolumab (NIVO) in patients with virus-associated tumors (CheckMate 358): efficacy and safety in Merkel cell carcinoma (MCC)**.** Cancer Res 2017, 77**:**CT074-CT074.
20. Schadendorf D, Wolchok JD, Hodi FS, Chiarion-Sileni V, Gonzalez R, Rutkowski P, et al. Efficacy and Safety Outcomes in Patients With Advanced Melanoma Who Discontinued Treatment With Nivolumab and Ipilimumab Because of Adverse Events: A Pooled Analysis of Randomized Phase II and III Trials. J Clin Oncol. 2017;35(34):3807-14.

21. Tai PT, Yu E, Winquist E, Hammond A, Stitt L, Tonita J, et al. Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. J Clin Oncol. 2000;18(12):2493-9.
22. Topalian SL, Bhatia S, Amin A, Kudchadkar RR, Sharfman WH, Lebbe C, et al. Neoadjuvant Nivolumab for Patients With Resectable Merkel Cell Carcinoma in the CheckMate 358 Trial. J Clin Oncol. 2020:Jco2000201.