Acta Oncologica, 2011; 50: 479–480

informa
healthcare

LETTER TO THE EDITOR

Use of interferon-alpha in two patients with Merkel cell carcinoma positive for Merkel cell polyomavirus

CAROLINE BIVER-DALLE[1,2], THIERRY NGUYEN[3], ANTOINE TOUZÉ[4], CLARISSE SACCOMANI[1,2], SÉVERINE PENZ[1,2], SANDRINE CUNAT-PEULTIER[1,2], MARIE-ODILE RIOU-GOTTA[1,2], PHILIPPE HUMBERT[2], PIERRE COURSAGET[4] & FRANÇOIS AUBIN[1,2]

[1]*Université de Franche Comté, EA3181, IFR133, Besançon, France,* [2]*Centre Hospitalier Universitaire, Service de Dermatologie, Besançon, France,* [3]*Centre Hospitalier Universitaire, Service d'Oncologie, Besançon, France and* [4]*Université F. Rabelais, INSERM U618, Tours, France.*

To the Editor

Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer that occurs most frequently in the elderly on sun-exposed sites. A new virus belonging to the *Polyomaviridae* family and named Merkel cell polyomavirus (MCPyV) has recently [1] been identified in tumor tissues from patients with Merkel cell carcinoma (MCC). Furthermore, interferon-alpha (IFN) demonstrated an *in vitro* anti-tumor effect on Merkel cells [2]. Based on these findings, we decided to treat two patients with unresectable stage III MCC positive for MCPyV with IFN as a broad-spectrum antiviral agent [3].

Case Reports

An 84-year-old man developed a MCC on the right shoulder which was removed in February 2009. Adjuvant radiotherapy was started. One month later, a palpable right axillary lymph node was noted by the patient. Radical axillary lymph node dissection confirmed the MCC metastasis. Adjuvant radiotherapy on the primary site was resumed and initiated on the right axilla. However, one month later, multiple unresectable distant subcutaneous metastases occurred. Carboplatine and etoposide were then introduced. At day 5, the patient developed a severe Gram-negative septic shock. After combined antibiotherapy (Piptazobactam and Amikacin) and the removal of the Port-A-Cath, patient recovered and refused any further chemotherapy. Presence of MCPyV DNA was detected by PCR in both primary tumor and a subcutaneous metastasis [4], and serum was positive [5] for the presence of MCPyV antibodies (titer of 8 100). Based on these findings, we decided to introduce IFN-alpha-2b treatment (Roferon®-A, Roche, 3 MUI daily). After three weeks, the patient developed a severe asthenia and psychiatric manifestations despite the addition of non-steroid anti-inflammatory and antidepressant drugs. As there was no regression of the subcutaneous metastases, IFN treatment was discontinued at week 12. After a seven-month follow-up, the patient died with lung and liver metastases.

An 81-year-old woman presented with severe asthenia and abdominal pain for the last four months. Physical examination revealed a mass in the right upper quadrant, and a 3 cm tumor of the right groin area. CT scan showed multiple pancreatic and lung metastasis along with mediastinal and hilar lymph nodes. Histological evaluation of the groin tumor indicated lymph node metastases of MCC. Presence of MCPyV DNA was detected by PCR [4] with a viral load was one copy of MCPyV DNA per 100 cells [6]. Serum was also positive [5] for the presence of MCPyV antibodies (titer of 72 900). We introduced IFN-alpha-2b treatment (Roferon®-A, Roche, 3 MUI daily) in association with non-steroid anti-inflammatory and antidepressant drugs. However, three months later, the patient developed a severe asthenia with depression and an increase of abdominal pain. Abdominal MRI showed

Correspondence: François Aubin, Service de Dermatologie, Hôpital Saint-Jacques, 2 Place Saint-Jacques, 25030 Besançon Cedex, France. E-mail: francois.aubin@univ-fcomte.fr

(Received 8 June 2010; accepted 29 July 2010)

ISSN 0284-186X print/ISSN 1651-226X online © 2011 Informa Healthcare
DOI: 10.3109/0284186X.2010.512924

pronounced progression of all metastases with a thrombosis in the inferior vena cava. Interferon was then stopped and the patient received palliative care until her death two months later.

Discussion

Clonal integration of the MCPyV genome within tumor cell genome and the deletions or mutations within the TAg gene [1,6] suggest MCPyV has a direct oncogenic role, and that viral infection is an early event in MCC pathogenesis. Altogether these findings suggest the potential interest of antiviral strategies for MCC treatment [2]. Among them, attention is focused on IFN-alpha because of its non-specific broad-spectrum antiviral and antitumoral effects. IFN-alpha belongs to type 1 IFNs, which mediate diverse biological effects, including regulation of innate and adaptative immune responses and antiproliferative activity [3]. To our knowledge, there is only one study demonstrating the *in vitro* anti-tumor activity of IFN-alpha on Merkel cells through antiproliferative and pro-apoptotic effects [2]. The lack of effect of INF-alpha in our two cases raised several hypothesis. First, it is possible that the doses of IFN used were not suitable, or the duration of IFN treatment was not long enough to exert full antiviral and antitumoral effects. Second, recent studies suggest the biological heterogeneity of MCC [7], in terms of viral load and expression of oncogenic markers [8], and the level of MCPyV antibodies [9]. This could have an impact on the sensitivity to therapeutic responses. Third, MCPyV may require additional antiviral strategies such as other TLR stimulatory ligands, activators of IFN-inducible antiviral effectors and agents interfering with essential virus-host interactions. Besides the broad-spectrum antiviral drugs, more specific antiviral agent may also be considered, such as cidofovir.

Conclusion

In conclusion, although the lack of efficacy of IFN in our preliminary experience, the etiological link between MCPyV and MCC suggests that new therapeutic strategies should be evaluated in regard with the advancing knowledge of MCPyV virus biology.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008;319:1096–100.

[2] Krasagakis K, Krüger-Krasagakis S, Tzanakakis GN, Darivianaki K, Stathopoulos EN, Tosca AD. Interferon-alpha inhibits proliferation and induces apoptosis of merkel cell carcinoma in vitro. Cancer Invest 2008;26:562–8.

[3] Burke JD, Fish EN. Antiviral strategies: The present and beyond. Curr Mol Pharmacol 2009;2:32–9.

[4] Touzé A, Gaitan J, Maruani A, Le Bidre E, Doussinaud A, Clavel C, et al. Merkel cell polyomavirus strains in patients with merkel cell carcinoma. Emerg Infect Dis 2009;15: 960–2.

[5] Touzé A, Gaitan J, Arnold F, Cazal R, Fleury MJ, Combelas N, et al. Generation of Merkel cell polyomavirus virus-like particles and their application to the detection of MCV antibodies. J Clin Microbiol 2010;48:1767–70.

[6] 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;218:48–56.

[7] Shuda M, Feng H, Kwun HJ, Rosen ST, Gjoerup O, Moore PS, et al. T antigen mutations are a human tumor-specific signature for Merkel cell polyomavirus. Proc Natl Acad Sci USA 2008;105:16272–7.

[8] Bhatia K, Goedert JJ, Modali R, Preiss L, Ayers LW. Merkel cell carcinoma subgroups by Merkel cell polyomavirus DNA relative abundance and oncogene expression. Int J Cancer 2010;126:2240–6.

[9] Pastrana DV, Tolstov YL, Becker JC, Moore PS, Chang Y, Buck CB. Quantitation of human seroresponsiveness to Merkel cell polyomavirus. PLoS Pathog 2009;5:e1000578.