Oncolytic immunotherapy

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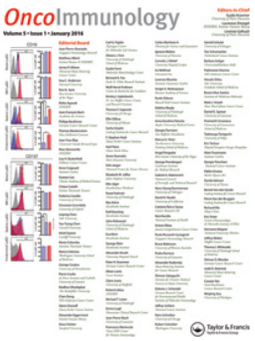

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EDITORIAL

Oncolytic immunotherapy: The new clinical outbreak

Jean-François Fonteneau[a], Carole Achard[a], Cécile Zaupa[b], Johann Foloppe[b], and Philippe Erbs[b]

[a]INSERM UMR892, CNRS UMR6299, Université de Nantes, Nantes, France; [b]TRANSGENE SA, Illkirch-Graffenstaden, France

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This last year was productive for the oncolytic viruses (OV) field with numerous advancements. The 9th international conference on OV therapeutics, that has been held in Boston, USA, from the 13th to the 16th of June 2015, was the opportunity to discuss these progresses (OVC Boston 2015: the conference program with abstracts and the list of participants is available at this address: http://ovcboston.com/final-program/). It was locally organized by Nino Chiocca from Brigham and Women's Hospital and Samuel Rabkin from Massachusetts General Hospital. OV are viruses that infect preferentially or exclusively cancer cells and cause immunogenic cell death which induces or stimulates an antitumor immune response in patients.[1,2] During this congress, many encouraging clinical results were presented.

T-vec from Amgen Inc. is a strain of Herpes simplex type I virus that was selected to infect tumor cells. It is modified to encode the granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate immunity and the US11 protein to increase viral replication. It is also deleted of two virulence factors, ICP47 and ICP34.5. Results of a phase III clinical trial where T-vec was used to treat metastatic melanoma patients were recently published in the Journal of Clinical Oncology.[3] At the end of May 2015, the positive clinical benefits observed in this study led a panel of experts of the food and drugs administration (FDA) to vote for the use of T-vec in the treatment of metastatic melanoma with a large majority (22 against 1). Since October the 27th, 2015, T-vec is the first OV approved by the FDA for the treatment of melanoma.

These last years, immunotherapy of cancer has been improved by the use of checkpoint inhibitors (CPI) that are targeted therapies directed against molecules such as CTLA-4 or PD1 that inhibit the tumor cell recognition and lysis by cytotoxic T cells.[4] At the conference, Robert Andtbacka presented preliminary results of a phase I clinical trial where T-vec is associated with ipilimumab, a CPI targeting CTLA-4, in the treatment of metastatic melanoma. Clinical responses are better than that would be expected from the individual treatments. A Phase II comparing ipilimumab plus T-vec with ipilimumab alone is started.

Attenuated strain of measles viruses (MV) are also promising OV.[5] MV infects and kills tumor cells that express the entry receptor CD46 and that are deficient in the antiviral type I IFN response. The use of Edmonston strain of MV is evaluated for the treatment of several malignancies at the Mayo Clinic in Rochester, USA, by the teams of Eva Galanis and Stephen Russell. Eva Galanis presented results of phase I clinical trials for the treatment of ovarian cancer using either MV encoding the sodium/iodide symporter (MV-NIS) or the carcinoembryonic antigen (MV-CEA).[6] MV-NIS or MV-CEA were injected repeatedly in the peritoneal cavity of MV-seropositive patients. Replication of MV-NIS is followed by ^{123}I SPECT/CT imaging after ^{123}I injection. Replication of MV-CEA is monitored by RT-PCR against CEA on peritoneal fluid samples. Replication of both viruses was observed after injections. Median overall survival of patients receiving low doses of MV-CEA was 10.6 months compared to 29.3 months for those receiving high doses of MV-CEA or MV-NIS. Furthermore, in this study, an induction of a T cell response against tumor antigens was observed after treatment. A phase II is now started comparing MV-NIS to chemotherapy.

Stephen Russell presented an update of the phase I clinical trial for the treatment of MV-seronegative patients with metastatic multiple myeloma. The patient he described in its paper of May 2014,[7] who was alive 6 months after the treatment, is still alive today, 24 months after treatment. Stephen Russell also discussed the use of a vesicular stomatitis virus (VSV) encoding IFN-β.

Hardev Pandha provided an update on the clinical phaseI/II of CAVATAK CVA21, an oncolytic coxsackievirus, positive-sense single-stranded RNA picornavirus that binds to the N-terminal domain of ICAM-1, which is highly expressed on many solid tumors.[8] This phase I/II study is investigating the tolerance of multiple escalating intravenous doses of CVA21 in advanced cancer patients. To date, multiple CVA21 infusions have been generally well tolerated, and preliminary data indicate possible viral replication within tumor. Gough Au presented significant antitumor activity mediated by the combination of CVA21 and CPI (anti-PD1 and anti-CTLA4) in the murine B16 melanoma model and clinical evaluation of CVA21 in combination with anti-CTLA4 in advanced melanoma patients is currently underway.

Preclinical results suggest that combination of PD-1 inhibition therapy with Reolysin, that is an oncolytic reovirus evaluated in ongoing Phase III clinical trial,[9] confers significant survival benefit in a subcutaneous B16 melanoma model, by augmenting tumor-specific NK responses and specifically attenuating tumor-specific immunosuppression.

JX594 is a strain of vaccinia poxvirus modified by addition of the GM-CSF gene and deletion of the thymidine kinase gene. The replication of this virus requires a thymidine kinase activity that can be found in tumor cells. A phase III clinical trial for the treatment of hepatocellular carcinoma with JX594

CONTACT Jean-François Fonteneau jean-francois.fonteneau@inserm.fr

is planned by SillaJen Biotherapeutics and Transgene SA after the encouraging clinical results of the phase II.[10]

Other encouraging clinical results, notably for the treatment of glioblastoma with different OV, were presented at the conference during two sessions dedicated to clinical trials. OV Basic research was also addressed such as the role of the tumor microenvironment on OV efficiency presented by John Bell,[11] and the role of the STING pathway in tumor development and the sensitivity of tumor cells to DNA OV presented by Glen Barber.[12] It is not our goal to list all advancements in the OV field that were presented at this conference. We therefore apologize to the authors of all the other studies presented at the conference that are not reviewed here.

To conclude, it is worth noting that all preclinical and clinical studies of combination of OV with CPI (anti-CTLA4, anti-PDL1 and anti-PD1) show a synergy of these two types of treatment. Thus, a consensus emerges to claim that OV are good CPI allies. Indeed, OV induce or increase the lymphocytic infiltrates in tumors and CPI treatment improves their cytotoxic activity. It was therefore proposed that, whenever possible, OV would be associated with CPI in clinical trials. Finally, it was also suggested that "oncolytic virotherapy" is renamed "oncolytic immunotherapy", given the importance of the induction/stimulation of an antitumor immune response in the OV efficacy.

A new outbreak of good news for the OV field is now expected in Vancouver, Canada, in 2016 for the 10th international conference on OV therapeutics.

Disclosure of potential conflicts of interest

JFF owns a patent on the use of a modified attenuated MV for antitumor virotherapy. CZ, JF and PE are full-time employees of Transgene (Illkirch-Graffenstaden, France).

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