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Commentary

A clinical trial investigating biodistribution and shedding of an oncolytic virus

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Oncolytic viruses (OVs) are an emerging class of antitumoral therapeutics, that combine selective cancer cell killing and an immunotherapeutic effect, by facilitating the recognition of tumor antigens by the immune system [1]. To the present day, only one replication-competent OV, based on herpes simplex virus type 1 (HSV-1), talimogene laherparepvec or T-VEC (IMLYGIC®, Amgen) has been approved for clinical use in the US and the EU by intralesional injection against metastatic melanoma [2]. T-VEC is a genetically modified OV, carrying deletions in the ICP 34.5 (γ34.5) gene (attenuating virulence, in particular in neurons), in the ICP47 (Us12) gene (enhancing, among other effects, antigen presentation), and expressing a therapeutic gene (the human granulocyte-monocyte colony stimulating factor, GM-CSF) [3]. Recent "real world" clinical data confirm the efficacy of T-VEC against melanoma beyond clinical trials [4]. Although T-VEC proved to be quite safe [5], the main adverse effects being flu-like symptoms and fatigue, concerns still remain about the pharmacokinetics of the recombinant virus and the possibility of its transmission to healthcare workers and close contacts of the treated patient. In an article in *EBioMedicine,* Andtbacka and colleagues report the results of a phase 2 clinical trial investigating biodistribution, shedding and transmissibility of T-VEC in 60 patients with melanoma [6]. Following administration, injected lesions were covered with occlusive dressing according to the therapeutic protocol. Presence of viral DNA was assessed by a T-VEC specific quantitative real time PCR in blood, urine, swabs from injected lesions, exterior of dressings, oral and anogenital mucosa. Positive swabs were further tested for the presence of infectious virus. Close contacts of patients who developed suspect herpetic lesions were also tested. Interestingly, T-VEC DNA was detectable in the blood of most patients and in 31.7% urine samples during the first cycles of therapy, irrespective of previous HSV-1 serological status, while only a minority of patients was positive in oral (8.3%) and anogenital swabs (8%). During the following cycles of treatments and safety follow-up controls T-VEC specific PCR became rapidly negative. Of note and not surprisingly, the surface of the injected lesions resulted positive for viral DNA in 100% of patients at least once during cycles 1 to 4, and in 14% of patients during safety follow-up visits. Exterior of occlusive dressings was also positive in 80% of patients during cycles 1 to 4. Finally, only a small percentage of swabs obtained from the surface of injected lesions (7 out of 740 samples) was positive for infectious virus.

Three patients had cutaneous herpetic lesions with detectable T-VEC DNA from uninjected sites. Three close contacts had possible herpetic lesions. One of them declined testing, while the other two resulted PCR negative. One healthcare provider had a suspect lip lesion, which was also negative for T-VEC. The Authors also report overall safety and efficacy data. Most patients had adverse effects consisting mainly of chills (65%) and fatigue (56.7%). Serious related adverse effects were reported in 8 patients, and treatment was permanently discontinued in 3 patients.

The reported overall response rate (ORR) was 35%. Remarkably, 9 patients (15%) had a complete response, while 12 patients (20%) had a partial response, consistent with data of previous clinical trials [7].

Overall the reported results confirm the safety profile of T-VEC and, most importantly, the very low possibility of transmission to contacts and healthcare workers, when recommended precautions and protocols are applied. An issue that could require further inquiry is the presence of T-VEC DNA in the blood of most patients at the beginning of treatment. Even though it seems unlikely that a transient presence of DNA mirrors a real "viremia" with possible effects on metastases, this possibility should be evaluated, together with other systemic effects of the virus (for example, on the inflammatory response and modulation of the immune system). A remaining open question involves the *in vivo* kinetics of the expression of the T-VEC therapeutic gene (GM-CSF), which could be interesting both for the evaluation of its effect and for comparison with therapeutic genes expressed by other investigational HSV-1 based OVs.

T-VEC indeed represents a valuable tool in the treatment of melanoma, and it has been shown to synergize with immune checkpoint inhibitors (ICIs) in clinical trials [8], in particular in those tumors with a low baseline lymphocyte infiltrate that are poorly responsive to ICI monotherapy. On the other hand, the full therapeutic potential of OVs is probably still to be unleashed. Thus, the research goes on with different aims, such as devising OVs (i) that can be delivered systemically [9], (ii) that require an inferior number of injections, or (iii) that can extend their immunotherapeutic potential beyond melanoma, to other

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malignancies with a dismal prognosis and a poor response to immunotherapy [10]. In this setting, OVs are very attractive as a possible *trait d'union* between direct cancer cell lysis, immunotherapy and gene therapy.

Disclosure

The authors have nothing to disclose.

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