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Cancer immunotherapy turns viral

Lorenzo Galluzzi[1,2,3,†] and Enrico Lugli[4,*,†]

[1]Université Paris Descartes/Paris V; Sorbonne Paris Cité; Paris, France; [2]Equipe 11 Labelisée par la Ligue Nationale Contre le Cancer; Centre de Recherche des Cordeliers; Paris, France; [3]Institut Gustave Roussy; Villejuif, France; [4]Unit of Clinical and Experimental Immunology ; Humanitas Clinical and Research Institute; Rozzano, Italy

[†]These authors share senior authorship.

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Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; HSV, herpes simplex virus

The holy grail of anticancer therapy is to selectively eradicate malignant cells while sparing their normal counterparts. Tremendous progresses have been made in this sense during the past decade, as demonstrated by the development and subsequent integration into the clinical routine of ever more effective and safe therapeutic agents.[1] Among these, chemical inhibitors of oncogenic drivers such as vemurafenib (an inhibitor of mutated BRAF currently employed for the treatment of melanoma),[2,3] and highly specific monoclonal antibodies such as trastuzumab (an ERBB2-targeting antibody nowadays used for the treatment of several ERBB2$^+$ solid tumors including breast carcinoma)[4-6] have contributed to significantly decrease the side effects associated with antineoplastic regimens and, simultaneously, to increase their therapeutic potential.[1]

Thus, the introduction of targeted anticancer agents has considerably improved the life expectancy of (at least some subsets of) cancer patients. In most cases, however, the therapeutic benefits of this approach are paradoxically limited by its own specificity. Indeed, only a few tumor types, when not a single one, can be successfully treated with a highly specific chemo- or immunotherapy, owing to the restricted expression pattern of the drug target.[7,8] Moreover, cancer cells can adapt quite rapidly to a very specific selective pressure, such as that posed by targeted anticancer agents, by downregulating one (or a few) protein(s), a mechanism that also intervenes in the escape of tumor cells from immunosurveillance.[9] Conversely, traditional chemotherapeutics—which are generally employed as a first-line treatment against a variety of tumors—exert antineoplastic effects by targeting functions that are preferentially, but not exclusively, present in tumor cells. As a consequence, these cytotoxic chemicals are frequently associated with mild to moderate adverse reactions in a consistent proportion of patients. The identification of agents that preferentially kill cancer cells remains therefore subject of intense investigation.

The notion that viruses may constitute specific antineoplastic agents is not particularly novel, but oncolytic virotherapy has emerged only recently as an actual therapeutic alternative.[10] A large panel of viruses has been tested and genetically engineered in this sense, including (but not limited to) the herpes simplex virus (HSV), the Newcastle disease virus and several distinct adenoviruses.[11] Oncolytic viruses mediate antineoplastic effects by preferentially infecting and killing cancer cells while simultaneously activating a tumor-specific immune response.[10,11] Early attempts to exploit viruses as antineoplastic agents were not especially promising, as naturally occurring viral strains exhibit a limited selectivity for malignant cells and often result in disseminated infections as they spread to neighbor, non-malignant tissues. The advent of recombinant DNA technology allowed for the genetic engineering of viral strains with improved specificity and immunostimulatory potential.[12] HSV was among the first viruses to be characterized and developed for oncolytic virotherapy, owing to the facts that was genetically well characterized, exhibits an elevated lytic potential and is relatively safe for use in humans. More than ten years ago, Kucharczuk et al. developed a genetically engineered variant of HSV-1, HSV-1716, which is unable to replicate in normal post-mitotic cells owing to the deletion of RL1 (coding for the neurovirulence factor ICP34.5).[13] A few years later, BioVex Limited, now part of Amgen, developed a second-generation HSV-1 variant that lacks not only RL1 but also the gene coding for ICP47, another neurovirulence factor that primarily functions to inhibit antigen presentation by infected cells.[14] The virus was also engineered to drive the secretion of the immunostimulatory cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF),[14] mainly intended at recruiting immune cells at the site of infection.[15]

On March 19th, 2013, Amgen announced encouraging results of a Phase III clinical trial testing the antineoplastic activity of this recombinant virus, talimogene laherparepvec, in melanoma patients. In previous Phase I and II clinical trials, the biweekly intratumoral administration of talimogene laherparepvec (formerly known as OncoVEX^{GM-CSF}) to patients with various solid tumors, including unresectable melanoma, was well tolerated.[16,17] At the injection site, tumor cell necrosis coupled to a local inflammatory reaction involving the expression of GM-CSF and the recruitment of various immune cells was documented.[16] In addition, the administration of talimogene laherparepvec to melanoma patients was associated with an overall response rate, according to the Response Evaluation Criteria In Solid Tumors (RECIST), of 26%,[17] prompting the initiation of

*Correspondence to: Enrico Lugli; Email: enrico.lugli@humanitasresearch.it
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several Phase III clinical studies, including OPTiM (OncoVEX$^{GM\text{-}CSF}$ Pivotal Trial in Melanoma, www.clinicaltrial.gov NCT00769704).[18]

This global, randomized, open-label Phase III trial enrolled more than 400 patients bearing unresectable Stage IIIB, IIIC or IV melanoma to evaluate the safety and therapeutic profile of intratumoral talimogene laherparepvec, as compared with subcutaneous GM-CSF. In a recent press release, Amgen's investigators reported a significant difference in the durable response rate, defined as the rate of complete or partial response lasting continuously for at least six months, between the talimogene laherparepvec and the control arm (16% vs. 2%). Fatigue, chills and fever were the most prominent adverse events. Of note, overall survival data are not yet available, but are expected for the end of 2013.

These results suggest that oncolytic virotherapy may soon become an actual therapeutic option for the clinical management of melanoma. This said, there are several aspects that remain to be clarified for understanding whether oncolytic viruses may also be employed one day to treat other, less immunosensitive tumors. Several studies indicate indeed that the therapeutic effects of oncolytic viruses depend, at least in part, from the elicitation of tumor-specific immune responses.[12] In this sense, melanoma (together with renal cell carcinoma) surely constitutes a relatively privileged setting. Further studies will have therefore to elucidate whether oncolytic virotherapy is sufficient to trigger a therapeutic immune response against all types of solid tumors or whether—most likely—combinatorial regimens involving one or several immunostimulatory agents will be required to fully exploit the antineoplastic potential of oncolytic viruses.

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