DR. FRANCISCO BAUTISTA

Licenciado en medicina, especialista en pediatría y doctor en medicina.
Experiencia internacional de 5 años en centros de referencia europeos en oncología pediátrica.
Médico adjunto en el servicio de oncología pediátrica del H Niño Jesús.
Coordinador de la unidad de ensayos clínicos del H. Niño Jesús.
Expertise en desarrollo de nuevos fármacos en oncología pediátrica, metodología de la investigación, genética del cáncer y biología molecular.

VIRUS COMO TRATAMIENTO: DESDE LA PERSPECTIVA DE LA ONCOLOGÍA PEDIÁTRIA

Oncolytic viruses offer great promise in the field of immuno-oncology, with some products reaching late-phase clinical development for several adult cancers (Packiam et al. 2018) and one product (Imlygic / Talimogen laherparepvec / T-Vec) already approved for clinical use in melanoma (Poh 2016). A known limitation is the need for direct administration into the tumor, which poses significant challenges for central nervous system (CNS), thoracic and abdominal cancers and limits its use to easily injectable tumors such as melanoma (Rothermel et al. 2018), sarcomas (Cripe et al. 2015) or head and neck cancers (Harrington et al. 2010). As an example, intratumoral injection of DNX-2401 in adults with recurrent glioblastoma leaded to prolonged overall survival beyond 3 years in a significant proportion of patients as a result of a direct oncolytic effect followed by elicitation of an immune-mediated antiglioma response (Lang et al. 2018). While this approach may be suitable for patients with localized recurrent disease, most of the patients in the advanced setting will present with disseminated disease and in need of rather a systemic approach.

Oncolytic viruses administered intravenously (IV) in patients with metastatic tumors encounter nevertheless many physiological barriers before reaching cancer lesions. Repeated doses are equally threatened by the recognition and attack of the immune system. A “Trojan horse” strategy using carrier cells has been proposed to overcome the abovementioned limitations.

Our team at Hospital Niño Jesús has worked with autologous, bone marrow-derived mesenchymal stem cells (MSCs) as carrier of Icovir5, an oncolytic adenovirus (Cascalló et al. 2007; Alonso et al. 2007) resulting in a final product called Celyvir (García-Castro et al. 2010). MSCs may hide the virus from the recognition and attack of the innate and adaptive immune system before Celyvir delivers their load at the metastasis, favoring better conditions for the in situ oncolytic effect. Once the MSCs have eventually disappeared due to completion of adenoviral cycle, the increased oncolysis that would ensue should increment the chances for the initiation or reactivation of an antitumor immune response.

We have conducted preclinical studies testing sources of MSCs, cell doses, toxicities, in vivo tumor targeting capacity, antiadenoviral immune responses and antitumor effects using the Celyvir strategy in different animal models and a veterinary trial in canine patients with spontaneous cancer (Rincón et al. 2017; Cejalvo et al. 2018; Morales-Molina et al. 2018; Franco-Luzón et al. 2019). Tumor lesions were highly infiltrated by immune cells in the core of the tumor and the response rate of a veterinary trial with

Celyvir was high (74%), even with complete responses in animals with metastatic disease (14.8%) (Cejalvo et al. 2018).

We have conducted a first-in-man, first-in-child trial (NCT01844661) of Celyvir in adult and pediatric patients with relapsed or refractory solid tumors (Ramirez et al. 2018). Nine pediatric and eight adult patients (n=17) received treatment with Celyvir. Two pediatric patients (both diagnosed with metastatic neuroblastoma) had disease stabilization and seven had progressive disease. None of the adults responded. No ≥ Grade 2 related toxicities were observed, mainly fever. A positive PCR was found in most pediatric patients (78%) at a median of 2 infusions (range: 1-4) after initiating Celyvir, and most of them maintained adenoviral replication once detected for the first time (71%), suggesting that the carrier cells maintained the capacity for targeted delivery of the oncolytic adenoviruses upon repeated infusions

We are working in the development of two clinical trials with Celyvir with either allogenic or autologous MSC in several pediatric and adult tumor types.

A summary of current clinical trials exploring oncolytic viruses in pediatric patients with cancer is presented in Table 1 below.

Table 1. Current Recruiting Trials with Oncolytic Virus in Children with Cancer

Intervention	Population	Sponsor	Reference
G207 (HSV-1) + Radiotherapy	R/R CNS-tumors Age 3 to 18 years	Alabama University	NCT02457845
PVSRIPO (polio/rinovirus recombinant)	R/R CNS tumors Age 12 to 21 years	Istari Oncology, Inc.	NCT03043391
DNZ-2401	Newly diagnosed DIPG Age 1 to 18 years	Universidad de Navarra	NCT03178032

DIPG: Diffuse intrinsic pontine glioma; **CNS:** Central nervous system; **R/R:** Relapsed / Refractory

Source: www.clinicaltrials.gov (Accessed the 11th September 2019; only actively recruiting studies)