Cytotoxic activity of Dendrimer Nanoparticles and Dendrimer Drugs Formulations on Human Neuroblastoma Cells: Our Recent Update

Silvana Alfei [1,*], Barbara Marengo [2], Giulia Elda Valenti [2], Guendalina Zuccari [1], and Cinzia Domenicotti [2]

[1] Department of Pharmacy (DiFAR), University of Genoa, Viale Cembrano, 4 - I-16148 - Genoa, Italy; alfei@difar.unige.it; zuccari@difar.unige.it

[2] Department of Experimental Medicine - DIMES, University of Genoa, Via Alberti L.B. 2 I- 16132 Genoa, Italy; barbara.marengo@unige.it; giuliaelda.valenti@edu.unige.it; cinzia.domenicotti@unige.it

* Correspondence: alfei@difar.unige.it; Tel.: +39 010 3552296 (S.A.)

Human neuroblastoma (NB) is a pediatric tumor, which, after an initial response to therapy, usually develops resistance. Etoposide (ETO) which is a drug commonly used to clinically treat NB, exerts anticancer effects by increasing–reactive oxygen species (ROS) generation [1,2]. Similarly, gallic acid (GA), although not specifically in NB treatment, exerts pro-oxidant anti-cancer effects associated to low toxicity for healthy cells. Unfortunately, low stability, poor solubility and an unfavorable pharmacokinetic negatively influence ETO and GA efficacy [1, 2]. To address GA and ETO issues, biodegradable dendrimer nanoparticles (DNPs) were prepared for entrapping ETO [2], as well as for encapsulating and covalently binding GA, obtaining the drugs-loaded dendrimers ETOD, GALD and GAD [1, 2]. The cytotoxic activity of DNPs, GA, ETOD, GALD and GAD was tested on ETO-sensitive and ETO-resistant NB cells. Unexpectedly, DNPs were able to exert *per se* a ROS-mediated cytotoxic activity comparable to ETO, on both cell populations. ETOD, combining DNPs and ETO, showed a synergistic action of the two molecules, a slow release of the drug and a significantly improved protracted bioactivity [2]. Free GA proved a dose-dependent ROS-mediated cytotoxicity on both cell populations, but intriguingly, when administered in dendrimer formulations, at a dose not cytotoxic for NB cells, nullified any pro-oxidant activity of DNPs [1]. Collectively, DNPs could represent a platform to develop novel devices against NB, while ETOD could be a biodegradable device for the efficient delivery of ETO into NB cells. GALD and GAD, due to the presence of GA, were inactive on NB cells, but GA resized in nanoparticles and at very low dose has shown considerable ability in counteracting ROS production induced by DNPs, thereby exerting a possible protective action for healthy cells.

1. Alfei, S.; Marengo, B.; Zuccari, G.; Turrini, F.; Domenicotti, C. Dendrimer Nanodevices and Gallic Acid as Novel Strategies to Fight Chemoresistance in Neuroblastoma Cells. *Nanomaterials* **2020**, *10*, 1243.
2. Alfei, S.; Marengo, B.; Domenicotti, C. Polyester-Based Dendrimer Nanoparticles Combined with Etoposide Have an Improved Cytotoxic and Pro-Oxidant Effect on Human Neuroblastoma Cells. *Antioxidants* **2020**, *9*, 50.