CELLULAR PHARMACOKINETICS/PHARMACODYNAMICS OF DOXORUBICIN IN A WIDE ARRAY OF CELL LINES

MAXIME LE MERDY[1,2], HENDRIKS BS[3], and YANGUANG CAO[1]

Affiliation: 1: Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, New York, 14214, USA.

2: INSERM, UMR-S 1144, Paris F-75006, France; Université Paris Descartes, Université Paris Diderot, UMR-S 1144, Paris F-75013, France

3: Merrimack Pharmaceuticals, One Kendall Square, Suite B7201, Cambridge, MA 02139 USA.

Purpose: Doxorubicin (Dox) has been used in the treatment of a wide range of cancers and the mechanism underlying its anti-tumor effect is primarily related to intercalation with DNA duplex, leading to change of DNA conformation and death of tumor cells. Cardiotoxicity is one of its major dose-limiting side-effects. Liposomal Dox has shown improved therapeutic index with less cardiotoxicity and selective tumor deposition. However, the selective tumor deposition has not been successfully translated into clinical response. To further optimize this delivery system and understand factors responsible for this poor translation, a systems physiologically-based PK/PD model that integrates disposition and mechanism-of-action of both Dox and Liposomal Dox is believed to be crucial. As part of this systems model, we developed a cellular PK/PD model for Dox in a wide array of tumor cell lines.

Method and Approach: The data for cellular uptake of Dox in 19 cell lines (PK) was provided by Merrimack Pharmaceuticals and the data for Dox time- and concentration-dependent cytotoxic effect (PD) was obtained from the literature. A cellular PK/PD model was developed that considers Dox cell membrane transport, ionization extent, nucleus transport, DNA binding/unbinding, tumor cell proliferation, and DNA-complex-driven apoptosis (Figure 1). The model was developed in a stepwise manner with cellular PK optimized first as most cellular uptake data was obtained within 3 hours during which cell proliferation/apoptosis was insignificant. Model parameters were either derived from the literature (eg, pKa, Kd) or taken as physiologic values (eg. cell surface, cell volume). Only three parameters were optimized (cellular permeability rate (PER), nucleus permeability rate (PER_N), and cell death (KeC)). Adapt-5 was used for model simulation and optimization.

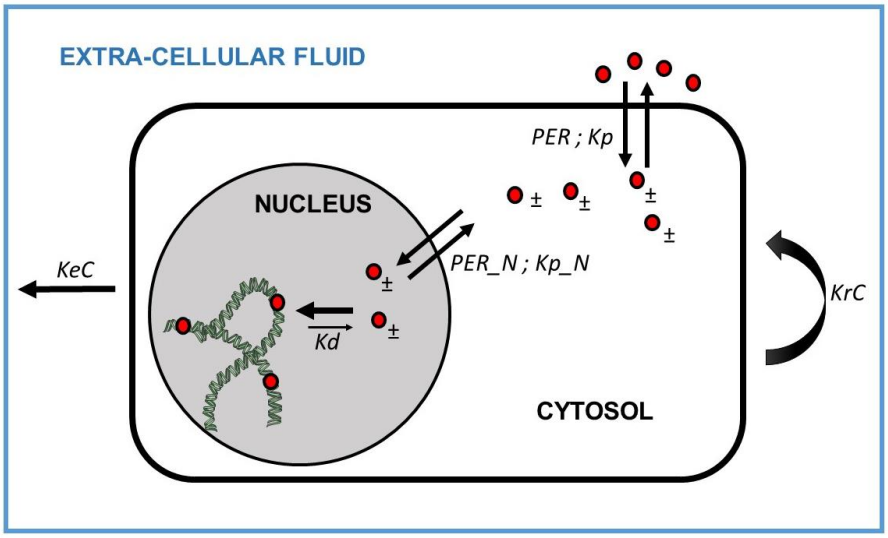

Figure 1: Proposed PK/PD model for Dox in a wide array of cancer cell lines.

Results: The integrated cellular PK/PD can reasonably predict Dox cell distribution kinetics and its time- and concentration-dependent cytotoxic effect. The optimized parameters values are 0.013 cm/hr

for PER, 0.04 cm/hr for PER_N, and 0.0027 /hr, for for KeC for the OVCAR8 cell line. Dox intercalation with DNA duplex was suggested as a fast process and the high DNA concentrations resulted in appreciable Dox accumulation in nucleus. The cytotoxic effects were nicely predicted by the accumulated DNA adduct in this model, consistent with the Dox primary mechanism of action.

Conclusion: A cellular PK/PD model for Dox that incorporates a cascade of steps from cellular uptake, to DNA intercalation, eventually to cell apoptosis seems useful to evaluate Dox cellular transport and kinetics, and make mechanistic predictions of its cytotoxic effect. This model will be further extended into depicting Dox system disposition in a variety of species

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