Applied Mathematics Letters 24 (2011) 1251–1256

Contents lists available at ScienceDirect

Applied Mathematics Letters

journal homepage: www.elsevier.com/locate/aml

Theoretical optimization of Irinotecan-based anticancer strategies in the case of drug-induced efflux

Annabelle Ballesta [a,b,c,*], Jean Clairambault [a,b,c], Sandrine Dulong [b,c], Francis Levi [b,c,d]

[a] INRIA Rocquencourt, BANG project team, Domaine de Voluceau BP105, 78153 Le Chesnay Cedex, France

[b] INSERM, U776 "Rythmes biologiques et cancers", Hôpital Paul Brousse, 91405 Villejuif, France

[c] Université Paris-Sud, UMR-SO776, 91405 Orsay, France

[d] Assistance Publique - Hôpitaux de Paris, Unité de Chronothérapie, Département d'oncologie médicale, Hôpital Paul Brousse, Villejuif, France

ARTICLE INFO

Article history:
Received 3 February 2011
Accepted 22 February 2011

Keywords:
Molecular modeling
Anticancer drug
Pharmacokinetics–pharmacodynamics
Therapeutics optimization
Drug-driven transporter induction

ABSTRACT

The anticancer drug Irinotecan (CPT11) is known to trigger the induction of ATP-Binding Cassette (ABC) transporters, responsible for the efflux of the drug and its metabolites outside of the cells. The drug-modulated overexpression of those transporters prevents its accumulation in the intracellular medium, therefore decreasing its efficacy. A critical clinical concern lies in the design of CPT11-based therapeutic strategies which eradicate a maximum number of cancer cells despite their ability to become resistant. In order to address this issue, we supplemented an existing mathematical model of CPT11 molecular pharmacokinetics–pharmacodynamics (PK–PD) with a new model of CPT11-induced overexpression of ABC transporters. We then theoretically optimized exposure to CPT11 given as a single agent or combined either with ABC transporter inhibitors, or with inhibitors of nuclear factors whose activation is responsible for transporter overexpression. We firstly considered a cancer cell population endowed with the ability of inducing their transporters. For any drug combination, we concluded that the highest concentration of CPT11 should be administered in order to kill a maximum number of cancer cells, despite the triggering of resistance. We then considered a population of healthy cells which were assumed to be identical to cancer cells except that they were not able to become resistant. Optimal schemes were defined as the ones which maximized DNA damage in cancer cells under the constraint of DNA damage in healthy cells not exceeding a tolerability threshold. The optimal therapeutic strategy consisted in combining CPT11 with ABC transporter inhibitors as it achieved a complete reversal of resistance by means of the lowest concentrations of CPT11.

1. Introduction

Multidrug resistance (MDR) is characterized by the ability of cancer cells to become simultaneously resistant to many anticancer drugs. A possible cellular mechanism of MDR is the drug-modulated induction of ATP-Binding Cassette (ABC) transporters which actively pump molecules outside of the cells [1]. The enhancement of ABC transporter expression in

Abbreviations: MDR, Multidrug resistance; ABC transporter, ATP-binding cassette transporter; CPT11, irinotecan; PK-PD, pharmacokinetics–pharmacodynamics; CES, carboxylesterases; UGT, UDP-glucuronosyltransferase; TOP1, topoisomerase 1; NF-κB, Nuclear factor κB; NRF-2, Nuclear factor (erythroid-derived 2)-like 2.

* Corresponding author at: INRIA Rocquencourt, BANG project team, Domaine de Voluceau BP105, 78153 Le Chesnay Cedex, France. Tel.: +33 0 1 39 63 58 86; fax: +33 0 1 39 63 58 82.

E-mail address: annabelle.ballesta@inria.fr (A. Ballesta).

0893-9659/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.aml.2011.02.017

tumor tissues prevents anticancer drugs from accumulating in the intracellular medium and therefore decreases their efficacy. Irinotecan (CPT11) is a cytotoxic drug approved for the treatment of colorectal cancer [2]. CPT11 is a substrate for several ABC transporters and is known to trigger their induction in cancer cell lines [3–5]. We propose here to theoretically optimize CPT11-based therapeutic strategies in the case of MDR.

To address this concern, we designed a mathematical model for CPT11-driven transporter induction by extending an existing model of CPT11 molecular pharmacokinetics–pharmacodynamics (PK–PD) [6]. We then theoretically investigated optimal therapeutic strategies which circumvent resistance in cancer cells. We firstly searched for exposure schemes which maximized DNA damage within a population of cancer cells endowed with the ability of inducing their transporters. Then we considered a second population defined as healthy cells which were identical to the cancer ones except that they were not endowed with the considered resistant mechanism. Optimal exposure schemes were defined as the ones that maximized DNA damage in cancer cells under the constraint of DNA damage in healthy cells not exceeding a tolerability threshold. We investigated three drug combinations: CPT11 given as a single agent, combined with ABC transporter inhibitors, or combined with inhibitors of nuclear factors whose activation is responsible for ABC transporter induction.

2. The existing mathematical model of CPT11 molecular PK–PD

A mathematical model of CPT11 molecular PK–PD was previously built and fitted to *in vitro* experimental data [6]. It describes molecular events occurring within a cell population during CPT11 exposure. Briefly, CPT11 in the intracellular medium (CPT_{in}) is converted into its active metabolite SN38 (SN_{in}) under the catalytic activity of carboxylesterases (CES). SN38 is deactivated into SN38G through UDP-glucuronosyltransferase enzymes (UGT) [2]. CPT11, SN38 and SN38G are assumed to enter passively into the cytoplasm but to be actively expelled outside of the cells by several transporters of the ABC superfamily. The variable ABC_CPT represents transporters responsible for CPT11 efflux and stands for the cumulative activity of ABCB1, ABCC1 and ABCC2. Transporters of SN38 and SN38G are denoted by the variable ABC_SN which represents the activity of ABCC1, ABCC2 and ABCG2 [6].

$$\frac{\mathrm{d}[CPT_{in}]}{\mathrm{d}t} = k_{upCPT}[CPT_{out}] - \frac{V_{effCPT}[ABC\_CPT][CPT_{in}]}{K_{effCPT} + [CPT_{in}]} - \frac{V_{ces}[CES][CPT_{in}]}{K_{ces} + [CPT_{in}]} \tag{1}$$

$$\begin{aligned}\frac{\mathrm{d}[SN_{in}]}{\mathrm{d}t} &= k_{upSN}[SN_{out}] - \frac{V_{effSN}[ABC\_SN][SN_{in}]}{K_{effSN} + [SN_{in}]} + \frac{V_{ces}[CES][CPT_{in}]}{K_{ces} + [CPT_{in}]} \\ &\quad - \frac{V_{ugt}[UGT][SN_{in}]}{K_{ugt} + [SN_{in}]} - k_{f2}[DNATOP1][SN38_{in}] + k_{r2}[Compl].\end{aligned} \tag{2}$$

CPT11 is an inhibitor of topoisomerase 1 (TOP1), an enzyme which relaxes supercoiled DNA by creating transient single-stranded breaks [7]. The active metabolite SN38 stabilizes DNA/TOP1 complexes into reversible SN38/TOP1/DNA ones ($Compl$) which still spontaneously dissociate but at a much slower rate. Collisions between those ternary complexes and replication or transcription mechanisms create irreversible DNA damage ($Icompl$) which trigger DNA repair, cell cycle arrest and lead possibly to apoptosis [7]. $Icompl$ is the output variable of the model as it has been experimentally correlated with CPT11 cytotoxicity [6].

$$\frac{\mathrm{d}[Compl]}{\mathrm{d}t} = k_{f2}[DNATOP1][SN_{in}] - k_{r2}[Compl] - k_{Irr}[Compl] \tag{3}$$

$$\frac{\mathrm{d}[Icompl]}{\mathrm{d}t} = k_{Irr}[Compl]. \tag{4}$$

3. Adding CPT11-modulated ABC transporter induction

CPT11 exposure may enhance the expression of ABCB1 and ABCG2 both in cancer cell lines and in tumor tissues in patients [3–5]. Therefore we supplemented the existing mathematical model of CPT11 PK–PD with a representation of the drug-driven transporter induction.

A possible molecular mechanism leading to this induction consists in the activation by CPT11-induced DNA damage of nuclear factors which then promote the expression of ABC transporters (Fig. 1). Indeed, in cancer cell lines, DNA double-stranded breaks resulting from CPT11 exposure activate the nuclear factor NF-κB [8–10] which enhances ABCB1 expression [11,12]. In the same way, chemical stress may activate the nuclear factor NRF-2 which is known to promote the expression of ABCG2, ABCC1 and ABCC2 [13–16].

We thus propose the following model for mRNA and protein amounts of ABC transporters responsible for CPT11 and SN38 efflux:

$$\frac{\mathrm{d}[ABC\_X_{RNA}]}{\mathrm{d}t} = k_{fRNA} + k_{ind}\frac{[Icompl]^n}{th_{ind}^n + [Icompl]^n} - k_{dRNA}[ABC\_X_{RNA}] \tag{5}$$

$$\frac{\mathrm{d}[ABC\_X_{Prot}]}{\mathrm{d}t} = k_{fABC}[ABC\_X_{RNA}] - k_{dABC}[ABC\_X_{Prot}] \tag{6}$$

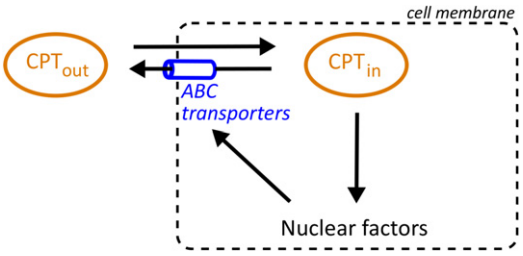

Fig. 1. CPT11-driven transporter induction CPT11 in the extracellular medium (CPT_{out}) enters passively in the cytoplasm (CPT_{in}). It is then actively expelled outside of the cells by efflux pumps called ABC transporters. CPT_{in} creates DNA damage responsible for the activation of nuclear factors which promote ABC transporter expression. The enhanced active efflux results in a decreased intracellular drug concentration and therefore confers resistance to the cells.

where *ABC_X* stands either for *ABC_CPT* or for *ABC_SN*. In the absence of CPT11, ABC transporter mRNA expression ABC_X_{RNA} is the result of transcription (k_{fRNA}) and degradation (k_{dABC}). ABC transporter proteins ABC_X_{Prot} arise from the translation of ABC_X_{RNA} (k_{fABC}) and are degraded by the cell (k_{dABC}). mRNA molecules were assumed not to be consumed by the translation mechanism as one mRNA molecule may produce several proteins.

Nuclear factor activation by CPT11 is phenomenologically modeled in Eq. (5) by an S-shaped function which shows a steep increase when DNA damage (*Icompl*) exceeds the induction threshold th_{ind}. Indeed experimental results show that CPT11 induces a rapid and transient activation of the nuclear factor NF-κB which is dose-dependent and rapidly saturates when the dose of CPT11 is increased [9,10]. This modeling choice results in a persistent overexpression of transporter mRNA and protein amounts which lasts after the drug exposure. Indeed the reversal of transporter induction was observed only after two months in cultured cell lines [4]. It is neglected here since our concern is to design *short-term* optimal exposure schemes.

For the sake of simplicity, we assumed that ABC_X_{RNA} and ABC_X_{Prot} are equal to 1 μM at steady state in the absence of drug and therefore set $k_{fRNA} = 1\ \mu\text{M}$, $k_{dRNA} = 1\ \text{h}^{-1}$ and $k_{fABC} = k_{dABC}$. We assumed that this is the first time that cells are exposed to CPT11. Therefore, at the initial instant, transporter mRNA and protein amounts are equal to 1. All other variables are equal to 0 except CPT11 extracellular concentration which is set to the chosen exposure concentration.

Other parameter values were estimated by fitting experimental data from the literature in which a 6-fold increase in ABCB1 mRNA level and a 2-fold increase in its protein amount were observed after 96 h of exposure to SN38 [3]. We assumed that these kinetics occurred for an exposure to 80 μM of CPT11 and obtained: $n = 20$, $k_{fABC} = k_{dABC} = 0.1\ \text{h}^{-1}$, $k_{ind} = 5\ \mu\text{M h}^{-1}$ and $th_{ind} = 0.13\ \mu\text{M}$.

4. Optimal therapeutic strategies in the case of MDR

4.1. Considered drug combinations

The aim of this part is to optimize CPT11-based therapeutics in the case of MDR. Clinical strategies aiming at reversing MDR mainly consist in inhibiting ABC transporters by pharmacological agents [1]. Another possibility inferred from mathematical modeling consists in inhibiting nuclear factors. Several inhibitors of NF-κB are currently under clinical studies [17]. Their administration in combination with CPT11 do enhance cell sensitivity to the drug. However, NF-κB displays a well-studied anti-apoptotic activity, which inhibition may be responsible for this increase in cell death [18,19]. We therefore considered three drug combinations: CPT11 given as a single agent, combined with ABC transporter inhibitors or combined with nuclear factor inhibitors.

CPT11 administration consisted in exposing cells to an extracellular medium containing the drug at an initial concentration ranging from 0 to 3000 μM. This interval of concentrations was chosen as it resulted in SN38 extracellular concentrations between 0 and 0.15 μM in the absence of transporter induction, which are physiological values for SN38 blood concentration in patients [20]. Exposure duration was searched between 1 and 168 h. Transporter or nuclear factor inhibitor administration was assumed to start before CPT11 exposure so that the system was at steady state when CPT11 was added to the culture medium. Nuclear factor inhibitors were modeled by setting k_{ind} to 0 for ABC_CPT and ABC_SN, which corresponds to a complete inhibition. ABC transporter inhibitors *I_ABC* were modeled as competitive inhibitors which irreversibly trap transporters into complexes:

$$\frac{[ABC\_X_{Prot}]}{dt} = k_{fABC} ABC\_X_{RNA} - k_{dABC}[ABC\_X_{Prot}] - k_{inhib}[I\_ABC][ABC_{Prot}] \tag{7}$$

$$\frac{[I\_ABC]}{dt} = -k_{inhib}[I\_ABC][ABC\_X_{Prot}]. \tag{8}$$

Inhibitor concentrations were assumed to be high enough to completely inhibit transporters in the absence of drug-driven induction. Therefore, ABC_CPT and ABC_SN were set to 0 at the initial instant. Inhibitor concentrations were set to 200 μM

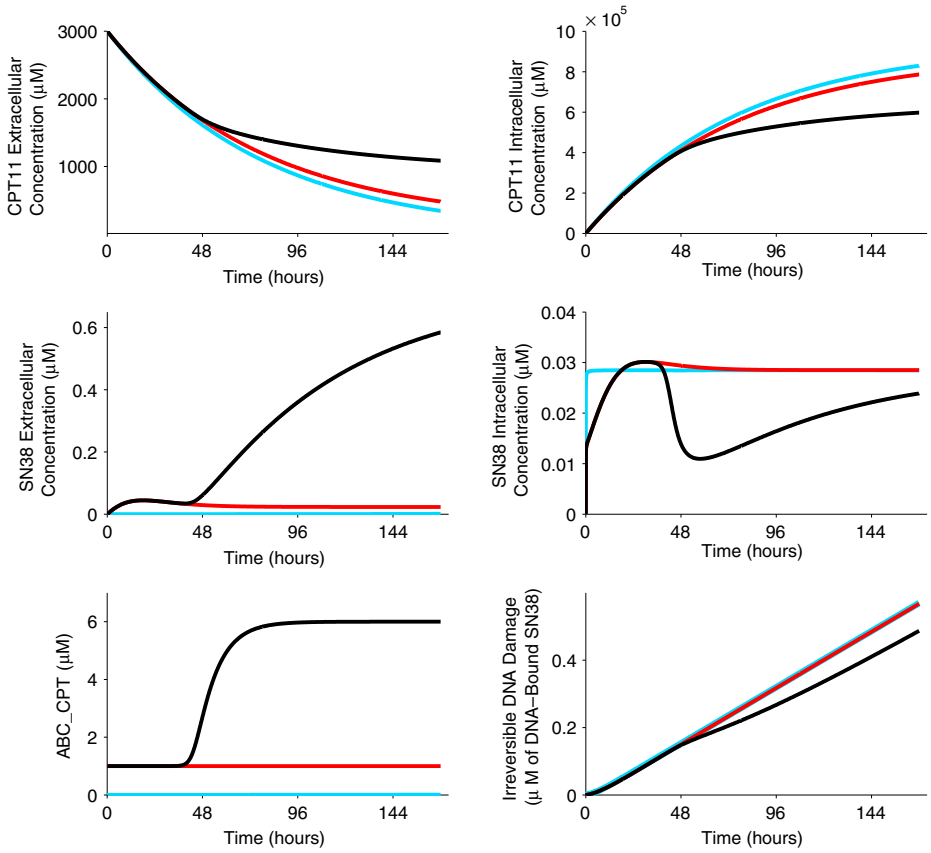

Fig. 2. Maximizing DNA damage in cancer cells without tolerability constraint. Time evolution of CPT11 and SN38 in intra and extracellular compartments, of ABC_CPT transporter protein amount and of the drug-induced irreversible complexes *Icompl*, during optimal exposure to CPT11 given as a single agent (black), combined with nuclear factor inhibitors (red), or with ABC transporter inhibitors (blue). For any drug combination, the optimal exposure scheme consisted in administering the highest concentration of CPT11 (3000 μM) over the longest duration (168 h). When CPT11 was administered as a single agent, cancer cells increased ABC transporter expression so that the intracellular concentrations of CPT11 and SN38 were decreased, and thus created less DNA damage. The co-administration of nuclear factor or ABC transporter inhibitors prevented transporter overexpression and increased CPT11-induced DNA damage. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

at initial instant and k_{inhib} was set to 1 so that the inhibition of transporter induction was rapid and complete. For each drug combination, the optimization procedure consisted in searching for the optimal concentration of CPT11 and the optimal exposure duration.

4.2. Maximizing DNA damage within cancer cells

First, we considered a population of cancer cells endowed with the mechanism of drug-driven transporter induction. We searched for exposure schemes which maximized DNA damage in these cancer cells without any tolerability constraint. The optimization procedure consisted in minimizing the opposite of the variable *Icompl* using the evolutionary algorithm CMAES [21].

For CPT11 given as a single agent, the optimal exposure scheme consisted in administering the highest concentration of 3000 μM over the longest duration equal to 168 h, despite the triggering of resistance (Fig. 2). This result thus suggests that cancer cells should be exposed to the highest tolerable dose of CPT11 so that the largest amount of DNA damage is created before they overexpress their transporters. The same optimal exposure scheme was found when CPT11 was co-administered with nuclear factor or transporter inhibitors, as no tolerability constraint was considered in this case. It can be noted that in the case of CPT11 given as a single agent, SN38 extracellular concentration was largely higher than when the drug was combined with inhibitors because SN38 enhanced efflux prevented its deactivation into SN38G which occurs in the intracellular medium.

4.3. Maximizing DNA damage within cancer cells under a constraint of tolerability

We then considered a population of healthy cells which were defined as identical to the previously mentioned cancer cells except that they were not endowed with the ability of enhancing ABC transporter expression in response to drug exposure.

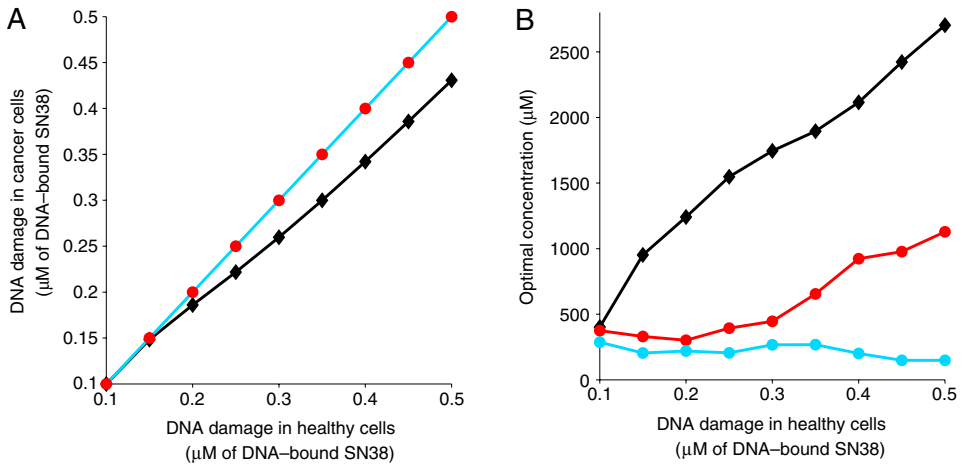

Fig. 3. Maximizing DNA damage in cancer cells with tolerability constraint Comparison of three therapeutic strategies: exposure to CPT11 as a single agent (black, diamond), combined with nuclear factor inhibitors (red, circle), or combined with ABC transporter inhibitors (blue, circle). **A.** DNA damage in cancer cells with respect to the maximal allowed DNA damage in healthy cells: combining CPT11 with inhibitors of nuclear factors or of ABC transporters completely reversed the resistance of cancer cells. **B.** Optimal concentrations with respect to maximal allowed DNA damage in healthy cells: optimal concentrations in the case of CPT11 combined with nuclear factor inhibitors were approximately half the ones found when CPT11 was given as a single agent. Combining CPT11 with ABC transporter inhibitors allowed a larger decrease in the optimal concentration to be administered. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Optimal exposure schemes were defined as the one that maximized DNA damage in cancer cells under the constraint of DNA damage in healthy cells not exceeding a tolerability threshold [6,22]. We determined optimal exposure schemes for a toxicity threshold ranging from 0.1 to 0.5 μM of DNA-bound SN38. The optimization procedure consisted in the minimization by the CMAES algorithm of a cost function which was the sum of two terms. The first term consisted in the opposite of DNA damage *Icompl* in cancer cells which typically ranged from 0 to 0.5 μM of DNA-bound SN38. The second term accounted for the toxicity constraint. It was equal to 0 when *Icompl* in healthy cells was under the tolerability threshold and became equal to 1000 otherwise. Optimization procedures gave the following results for each considered drug combination.

For any toxicity threshold, optimal exposure schemes when CPT11 was given as a single agent consisted in administering a concentration of 370–2700 μM over a duration ranging from 36–152 h, linearly increasing with the allowed toxicity (Fig. 3). When the toxicity threshold was lower than the resistance threshold (0.13 μM of DNA-bound SN38), DNA damage in healthy and cancer cells were the same since resistance was not triggered. On the contrary, when the induction threshold was exceeded, the optimal exposure schemes resulted in 12% more DNA damage in healthy cells than in cancer cells which triggered their resistance mechanism.

The combination of CPT11 with nuclear factor inhibitors allowed a decrease in optimal concentrations of CPT11 which were equal to approximately half the ones found when CPT11 was given as a single agent, optimal exposure durations remaining the same (Fig. 3). Moreover, the administration of nuclear factor inhibitors completely annihilated the advantage of resistant cells so that DNA damage in healthy and cancer cells were equal.

The use of ABC transporter inhibitors combined with CPT11 further decreased optimal concentrations of CPT11 to be administered which ranged between 150 and 290 μM (Fig. 3). Optimal durations were slightly decreased compared to the other drug combinations and linearly increased with the allowed toxicity from 32 to 148 h. This strategy also allowed a complete circumvent of resistance as DNA damage in healthy and cancer cells were equal. We therefore concluded that this strategy was the optimal one as it involved the lowest concentrations of CPT11 to completely reverse resistance.

5. Discussion

To the best of our knowledge, two other published works modeled ABC transporter induction. A mathematical model of doxorubicin PK–PD includes transporter overexpression which is assumed to be directly proportional to the intracellular drug concentration [23]. This modeling assumption does not render an account of the experimentally observed threshold on drug concentrations above which resistance is triggered. Moreover, this model allows the quantity of ABC transporters to grow to infinity in the case of large drug concentrations. Our modeling choice prevents ABC transporter amount to grow to infinity as the induction term rapidly reaches its maximal value k_{ind} when DNA damage *Icompl* increases.

Another work models the molecular PK–PD of 5-fluorouracil and includes the drug-induced transporter overexpression [20]. In this model, the nuclear factor remains activated as long as the drug intracellular concentration exceeds an induction threshold. However NF-κB kinetics in the presence of CPT11 consists in a transient activation of few hours which vanishes before the drug removal [9]. Furthermore, this modeling choice implies that killing a maximum number of cancer cells is achieved by an exposure to a dose below the induction threshold during a long period in order not to trigger the resistant

mechanism. On the contrary, our model concludes that the resistant mechanism is going to be triggered anyhow and that the highest tolerable dose should be given during the first cell exposure in order to kill a maximum number of cancer cells before they overexpress their transporters and become resistant.

This study concludes that combining ABC transporter inhibitors with CPT11 is the optimal therapeutic strategy as it involved the lowest concentrations of CPT11 to completely reverse MDR. However, we did not take into account the possible toxicity induced by the inhibitors themselves. Indeed several ABC transporter inhibitors display bone-marrow and neurological toxicity [1].

6. Conclusion

This article presents an extended model of CPT11 molecular PK–PD which includes the drug-induced transporter overexpression. The model predicted that, in order to kill a maximum number of resistant cells, the highest tolerable concentration of CPT11 should be administered during the first exposure, in order to create the largest amount of DNA damage when cells have not overexpressed their transporters yet. Now considering a tolerability constraint, we concluded that the combination of CPT11 with ABC transporter inhibitors was the optimal therapeutic strategy as it allowed a complete reversal of resistance by means of the lowest concentrations of CPT11.

References

[1] M.M. Gottesman, T. Fojo, S.E. Bates, Multidrug resistance in cancer: role of ATP-dependent transporters, Nat. Rev. Cancer 2 (1) (2002) 48–58.
[2] R.H. Mathijssen, R.J. van Alphen, J. Verweij, W.J. Loos, K. Nooter, G. Stoter, et al., Clinical pharmacokinetics and metabolism of irinotecan (CPT11), Clin. Cancer Res. 7 (8) (2001) 2182–2194.
[3] Y. Takeba, S. Sekine, T. Kumai, N. Matsumoto, S. Nakaya, Y. Tsuzuki, et al., Irinotecan-induced apoptosis is inhibited by increased *P*-glycoprotein expression and decreased p53 in human hepatocellular carcinoma cells, Biol. Pharm. Bull. 30 (8) (2007) 1400–1406.
[4] Y. Bessho, T. Oguri, H. Achiwa, H. Muramatsu, H. Maeda, T. Niimi, S. Sato, R. Ueda, Role of ABCG2 as a biomarker for predicting resistance to CPT-11/SN-38 in lung cancer, Cancer Sci. 97 (3) (2006) 192–198.
[5] L. Candeil, I. Gourdier, D. Peyron, N. Vezzio, V. Copois, F. Bibeau, et al., ABCG2 overexpression in colon cancer cells resistant to SN38 and in irinotecan-treated metastases, Int. J. Cancer 109 (6) (2004) 848–854.
[6] A. Ballesta, S. Dulong, C. Abbara, B. Cohen, A. Okyar, J. Clairambault, F. Levi, A combined experimental and mathematical approach for molecular-based optimization of irinotecan circadian delivery, PLoS Comput. Biol. (submitted for publication).
[7] Y. Pommier, Topoisomerase I inhibitors: camptothecins and beyond, Nat. Rev. Cancer 6 (10) (2006) 789–802.
[8] Y. Habraken, J. Piette, NF-kappaB activation by double-strand breaks, Biochem. Pharmacol. 72 (9) (2006) 1132–1141. Epub 2006 Sep 11.
[9] T.T. Huang, S.M. Wuerzberger-Davis, B.J. Seufzer, S.D. Shumway, T. Kurama, D.A. Boothman, S. Miyamoto, NF-kappaB activation by camptothecin. A linkage between nuclear DNA damage and cytoplasmic signaling events, J. Biol. Chem. 275 (13) (2000) 9501–9509.
[10] V. Bottero, V. Busuttil, A. Loubat, N. Magna, J.L. Fischel, G. Milano, J.F. Peyron, Activation of nuclear factor kappaB through the IKK complex by the topoisomerase poisons SN38 and doxorubicin: a brake to apoptosis in HeLa human carcinoma cells, Cancer Res. 61 (21) (2001) 7785–7791.
[11] M. Bentires-Alj, V. Barbu, M. Fillet, A. Chariot, B. Relic, N. Jacobs, J. Gielen, M.P. Merville, V. Bours, NF-kappaB transcription factor induces drug resistance through MDR1 expression in cancer cells, Oncogene 22 (1) (2003) 90–97.
[12] N. Kameyama, S. Arisawa, J. Ueyama, S. Kagota, K. Shinozuka, A. Hattori, et al., Increase in *P*-glycoprotein accompanied by activation of protein kinase Calpha and NF-kappaB p65 in the livers of rats with streptozotocin-induced diabetes, Biochim. Biophys. Acta 1782 (5) (2008) 355–360. Epub 2008 Mar 4.
[13] T. Adachi, H. Nakagawa, I. Chung, Y. Hagiya, K. Hoshijima, N. Noguchi, M.T. Kuo, T. Ishikawa, Nrf2-dependent and -independent induction of ABC transporters ABCC1, ABCC2, and ABCG2 in HepG2 cells under oxidative stress, J. Exp. Ther. Oncol. 6 (4) (2007) 335–348.
[14] A. Hayashi, H. Suzuki, K. Itoh, M. Yamamoto, Y. Sugiyama, Transcription factor Nrf2 is required for the constitutive and inducible expression of multidrug resistance-associated protein 1 in mouse embryo fibroblasts, Biochem. Biophys. Res. Commun. 310 (3) (2003) 824–829.
[15] J.M. Maher, X. Cheng, A.L. Slitt, M.Z. Dieter, C.D. Klaassen, Induction of the multidrug resistance-associated protein family of transporters by chemical activators of receptor-mediated pathways in mouse liver, Drug Metab. Dispos. 33 (7) (2005) 956–962. Epub 2005 Apr 15.
[16] I.M. Copple, C.E. Goldring, N.R. Kitteringham, B.K. Park, The keap1-nrf2 cellular defense pathway: mechanisms of regulation and role in protection against drug-induced toxicity, Handb. Exp. Pharmacol. (196) (2010) 233–266.
[17] S. Sebens, A. Arlt, H. Schafer, NF-kappaB as a molecular target in the therapy of pancreatic carcinoma, Recent Results Cancer Res. 177 (2008) 151–164.
[18] J.C. Cusack Jr., R. Liu, A.S. Baldwin Jr., Inducible chemoresistance to 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothe cin (CPT-11) in colorectal cancer cells and a xenograft model is overcome by inhibition of nuclear factor-kappaB activation, Cancer Res. 60 (9) (2000) 2323–2330.
[19] J. Guo, U.N. Verma, R.B. Gaynor, E.P. Frenkel, C.R. Becerra, Enhanced chemosensitivity to irinotecan by RNA interference-mediated down-regulation of the nuclear factor-kappaB p65 subunit, Clin. Cancer Res. 10 (10) (2004) 3333–3341.
[20] F. Levi, A. Okyar, S. Dulong, P.F. Innominato, J. Clairambault, Circadian timing in cancer treatments, Annu. Rev. Pharmacol. Toxicol. 50 (2010) 377–421.
[21] N. Hansen, The CMA evolution strategy: a comparing review. Towards a new evolutionary computation, in: Advances on Estimation of Distribution Algorithms, Springer, 2006, pp. 75–102.
[22] C. Basdevant, J. Clairambault, F. Levi, Optimisation of time-scheduled regimen for anti-cancer drug infusion, ESAIM:M2AN 39 (6) (2005) 1069–1086.
[23] K.T. Luu, J.A. Uchizono, *P*-glycoprotein induction and tumor cell-kill dynamics in response to differential doxorubicin dosing strategies: a theoretical pharmacodynamic model, Pharm. Res. 22 (5) (2005) 710–715. Epub 2005 May 17.