The AAPS Journal (2019) 21: 23
DOI: 10.1208/s12248-018-0291-9

Research Article

Translational Framework Predicting Tumour Response in Gemcitabine-Treated Patients with Advanced Pancreatic and Ovarian Cancer from Xenograft Studies

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Received 14 September 2018; accepted 17 December 2018; published online 31 January 2019

Abstract. The aim of this evaluation was to predict tumour response to gemcitabine in patients with advanced pancreas or ovarian cancer using pre-clinical data obtained from xenograft tumour-bearing mice. The approach consisted of building a translational model combining pre-clinical pharmacokinetic–pharmacodynamic (PKPD) models and parameters, with dosing paradigms used in the clinics along with clinical PK models to derive tumour profiles in humans driving overall survival. Tumour growth inhibition simulations were performed using drug effect parameters obtained from mice, system parameters obtained from mice after appropriate scaling, patient PK models for gemcitabine and carboplatin, and the standard dosing schedules given in the clinical scenario for both types of cancers. Tumour profiles in mice were scaled by body weight to their equivalent values in humans. As models for survival in humans showed that tumour size was the main driver of the hazard rate, it was possible to describe overall survival in pancreatic and ovarian cancer patients. Simulated tumour dynamics in pancreatic and ovarian cancer patients were evaluated using available data from clinical trials. Furthermore, calculated metrics showed values (maximal tumour regression [0–17%] and tumour size ratio at week 12 with respect to baseline [−9, −4.5]) in the range of those predicted with the clinical PKPD models. The model-informed Drug Discovery and Development paradigm has been successfully applied retrospectively to gemcitabine data, through a semi-mechanistic translational approach, describing the time course of the tumour response in patients from pre-clinical studies.

KEY WORDS: MID3; oncology; PKPD modelling; translational; tumour size.

BACKGROUND

The high attrition rates in oncology drug development (95%) not only increase the cost of research but also represent a delay in patients receiving safe, effective medications in a timely manner (1–3). To address this problem, scientists from both academia and industry are making great efforts to search for new strategies that would allow the success of a drug to be predicted from the early pre-clinical stages (4).

The pre-clinical phase of development is critical in the characterization of drug effects and their correlation with clinical data. One of the most common pre-clinical experiments in oncology consists of using human tumour xenografts to describe anti-tumour drug efficacy (5). Although the predictive capacity of xenograft studies has been widely discussed (6,7), recent publications highlight the benefits of applying the PKPD modelling framework to data gathered from these types of studies at the time of anticipating drug response in humans. As an example, Wong and colleagues (8) established the relationship between tumour growth inhibition (TGI) predicted using mouse-derived PKPD parameters, dosing schedules used in the clinic together with human PK, and clinical response. Additionally, Rocchetti *et al.* (5) predicted active doses in humans from pre-clinical PKPD models developed for animal TGI studies.

The first version of this manuscript was part of the thesis of Garcia-Cremades M and appears in dadun.unav.edu, a digital repository of the University of Navarra.

Electronic supplementary material The online version of this article (https://doi.org/10.1208/s12248-018-0291-9) contains supplementary material, which is available to authorized users.

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Gemcitabine (difluorodeoxycytidine; dFdC), a cytotoxic/cytostatic antimetabolite analog of cytidine nucleoside, is a pro-drug that has to be intracellularly metabolized to its active form (difluorodeoxycytidine triphosphate; dFdCTP) to exert its action. Once metabolized, its main mechanism of action consists of its incorporation into replicated DNA inducing the inhibition of cell growth and causing apoptosis (9,10). Gemcitabine is indicated for the treatment of several solid tumours, mainly given as single agent in the treatment of locally advanced or metastatic pancreatic cancer, or in combination in non-small-cell lung cancer (NSCLC), breast and ovarian cancer (9).

The recent development of pre-clinical (11) and clinical gemcitabine PKPD models for advanced pancreatic (12) and ovarian (13) cancer opens up the possibility of establishing a translational modelling approach, which in fact represents the goal of this study, that is to predict retrospectively clinical response to gemcitabine in patients using pre-clinical data obtained from xenograft tumour-bearing mice. The current evaluation aims to provide a general methodology of analysis and data interpretation beyond the specific case of gemcitabine.

METHODS

Figure 1a provides a high-level overview of the translational approach followed in the current evaluation, which combines pre-clinical PKPD models with clinical dosing paradigms and PK models to predict TGI for patients with advanced pancreatic and ovarian cancer.

Data

Raw tumour size (TS) data used to develop the PKPD models in humans (12,13) were available in the current study and served to evaluate the performance of the proposed translational approach.

Published PKPD Models

Pre-Clinical. The pre-clinical PKPD characteristics of gemcitabine administered as a single agent in pancreatic cancer xenografts or in combination with carboplatin in the case of ovarian cancer xenografts were extracted from a recently published model (11) represented by the following set of expressions:

$$dTV/dt = -\lambda_1 \times TV \times \mathrm{Log}(TV/K) - E_{\mathrm{Gem1}} \times TV \quad (1)$$

$$dK/dt = B \times TV - D \times K \times TV^{2/3} - (E_{\mathrm{Gem2}} + E_{\mathrm{Carbo}}) \times K \quad (2)$$

where TV is the tumour volume and K the carrying capacity (14) accounting for the nutrient supply required by the tumour to grow; λ_1 is a first-order rate constant that drives tumour proliferation; B and D are rate constants that control the stimulatory (B) and negative (D) feedback mechanisms of TV on K dynamics.

The effect of gemcitabine on TV shrinkage, which appeared delayed with respect to the pharmacokinetic profiles of drug concentrations in the plasma (Cp_{Gem}), was described by a linear pharmacodynamic model in pancreatic cancer and by an E_{MAX} pharmacodynamic model in ovarian cancer. These effects are represented by the term E_{Gem1} in the above-mentioned expressions. A chain of three transit compartments triggered by Cp_{Gem} and linked through a first-order rate constant (K_{TR}) was incorporated into the model to deal with the delayed effects. E_{Gem2} and E_{Carbo} correspond to the effects of gemcitabine and carboplatin on the carrying capacity which were found to be non-delayed with respect to the kinetic profiles of both drugs in the plasma and described using a linear pharmacodynamic model for the two cancer types. Original estimates of the model parameters obtained from the pre-clinical analysis are listed in Table I, and the schematic representation of the model is provided in Fig. 1b.

Clinical. Overall survival (OS) probabilities in patients with advanced pancreatic or ovarian cancer were previously characterized using a Weibull's distribution for the hazard rate (hz) of the form (12,13):

$$hz = \lambda \times \beta \times (\lambda \times t)^{\beta-1} \times e^{E_{Tumour}} \quad (3)$$

λ is the base parameter and β is the shape parameter of the Weibull's distribution. These estimates are dependent on the type of cancer. E_{Tumour} describes the effects of the tumour on hz and has the form of $\gamma_{\mathrm{p}} \times \log(TS)$ for pancreas cancer (12) and $\gamma_{\mathrm{o}} \times TS_{\mathrm{Ratio}}$ for ovarian cancer (13), where TS represents tumour size (cm) profile and TS_{Ratio} is the ratio between TS at each time point with respect to baseline until week 12 of treatment or at week 12 for longer times (13). Estimates of the λ, β, and γ parameters are also listed in Table I.

Predicting Tumour Size Profiles in Patients

The profile of TS in the clinical scenario was predicted following a four-step procedure: (a) generation of pharmacokinetic profiles, (b) calculation of the initial conditions of the tumour system, (c) simulation of tumour growth profiles, and (d) evaluation of the translational approach.

Step 1 *Pharmacokinetics*. Typical gemcitabine (parent drug) and carboplatin concentrations in the plasma were simulated based on previously developed PK models in patients (4,14) using the dosing schedules administered in the trials reporting the PKPD models in humans (12,13). Both PK models are comprised of two compartments, and the corresponding parameter values are also displayed in Table I. In the case of pancreatic cancer, a 30-min infusion of 1000 mg/m^2 of gemcitabine was given as a single agent once a week for 3 weeks in a 28-day cycle. For ovarian cancer, a 30-min infusion of 1000 mg/m^2 of gemcitabine was administered every week for 2 weeks in a 21-day cycle, in combination with carboplatin which was administered i.v. on the first day of each cycle at a dose corresponding to a target area under the curve (AUC) of 4 min mg/

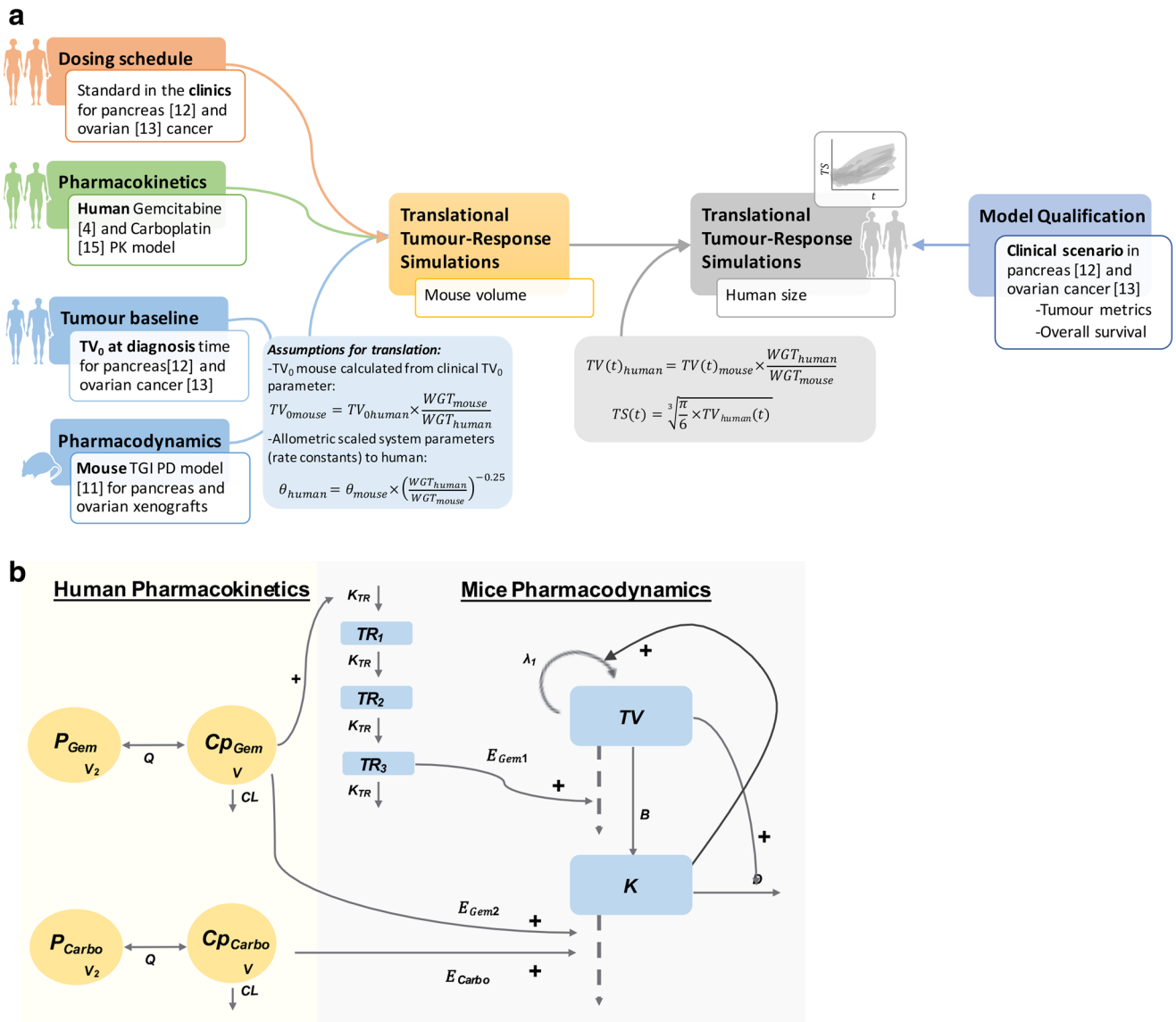

Fig. 1. **a** Flow chart representation of the translational model-based approach strategy used in the current analysis. **b** Schematic representation of the PKPD model structure. V, CL, V_2, and Q are the PK parameters for gemcitabine and carboplatin in humans (values reported in Supplementary material 1). P_{Gem} and P_{Carbo} represent the peripheral compartment of gemcitabine and carboplatin, respectively. TR_1, TR_2, and TR_3 represent the three transit compartments incorporated in the model for describing the delay in the apoptotic effect induced by gemcitabine. The rest of the parameters and model components are defined in the manuscript

mL. The actual dose used for carboplatin (492 mg) was calculated by multiplying the target AUC per the carboplatin clearance. The treatment duration consisted of 6 cycles for both cancer types.

Step 2 *Initial conditions of tumour system.* The PKPD models developed in mice xenografts (11) used volume to characterize tumour profiles while the PKPD models developed in cancer patients (12,13) used tumour size. Therefore, first, the typical estimates of TS at diagnosis (TS_0) with values of 61.7 and 69.7 mm obtained in patients with pancreas (12) or ovarian (13) cancer were transformed to tumour volumes (TV_0) under the assumption of a spherical tumour mass, $TV_0 = \pi/6 \times TS_0^3$ (15), resulting values of 113.3 (pancreas tumour) and 177.3 (ovarian tumour) cm^3. Then, TV_0 for both types of tumours was transformed to the animal scale using the ratio between mouse (25 g) and human (65 kg) body weights (WGT).

Carrying capacity is a cell line-dependent parameter in the pre-clinical model which modulates tumour growth (16). Estimates of K_0 (initial carrying capacity) reported by (11) were transformed using the ratio between TV_0 values obtained as described above and those estimated in mice.

Step 3 *Simulation of tumour growth profiles.* TS profiles were generated linking simulated human pharmacokinetic profiles (step 1) with the model developed in the pre-clinical scenario described

Table I. Table of Parameters of the Published Models Used in the Translational Exercise

	Parameter value						
Pharmacokinetic parameters reported in humans							
Gemcitabine two-compartment model							
CL (l/day/m^2)	2928						
v (l/m^2)	16						
Q (l/day/m^2)	3000						
v_2 (l/m^2)	47.4						
Carboplatin two-compartment model							
CL (l/day)	177						
v (l)	11.9						
Q (l/day)	2172						
v_2 (l)	8.23						
Survival models parameters reported in humans							
Pancreatic cancer							
λ_p	0.0126						
β_p(weeks^{-1})	1.63						
γ_p (log (cm)$^{-1}$)	0.618						
Ovarian cancer							
λ_o	0.036						
β_o(months^{-1})	1.99						
γ_{TSR}	0.893						
Disease–PKPD parameters reported in mice							
Tumour cell lines	KP4	ASPC1	MIAPACA2	PANC1	A2780	SKOVXLUC3_1	SKOVXLUC3_2
Disease progression parameters							
TV_0 (mm^3)	87.3	74.7	74	97	74.9	85.4	155
K_0 (mm^3)	1.13×10^{-2}	38.6	491	3×10^{-5}	82.6	116	116
λ_1 (day^{-1})	1.48×10^{-1}	1.82×10^{-1}	3.45×10^{-2}	2.52×10^{-2}	3.4×10^{-1}	4.07×10^{-2}	1.47×10^{-1}
B (day^{-1})	7.73×10^{-1}	2.98×10^{-1}	4.17×10^{-2}	3.08×10^{-1}	4.79×10^{-1}	4.47×10^{-1}	4.47×10^{-1}
D (day^{-1} mm$^{3-2/3}$)	1.2×10^{-3}	3.1×10^{-3}	0	0	1.27×10^{-3}	2.2×10^{-3}	2.2×10^{-3}
IIV_TV0 (%)	9	15	44	14	–	–	–
IIV_K0 (%)	14	29	85	20	–	–	–
IIV_λ_1 (%)	31	35	79	34	40	51	51
Gemcitabine effect parameters							
K_{TR} (day^{-1})	5.02	1.8×10^{-1}	1.93×10^{-1}	15.2	1.89×10^{-1}	6.1×10^{-1}	6.1×10^{-1}
$SLOPE_P$ (l/mg day)	4.2×10^{-1}	1.86×10^{-1}	3.26×10^{-2}	1.47×10^{-1}	–	–	–
Emax (day^{-1})	–	–	–	–	2.25	6.72×10^{-2}	6.72×10^{-2}
CE_{50} (mg/l)	–	–	–	–	2.6×10^{-1}	1.28×10^{-2}	1.28×10^{-2}
$SLOPE_O$ (l/mg day)	–	–	–	–	1.71×10^{-3}	1.71×10^{-1}	1.71×10^{-1}
IIV_K_{TR} (%)	19	10	90	26	–	–	–
IIV_SLOPE_O (%)	28	45	28	40	–	–	–
Carboplatin effect parameters							
$SLOPE_c$ (l/mg day)	–	–	–	–	5.44×10^{-1}	1.17×10^{-1}	1.17×10^{-1}

Pharmacokinetic parameters. CL; total plasma clearance, which for the case of gemcitabine represents the mean values across gender and age; V, apparent volume of distribution; Q, inter-compartment clearance; V_2, volume of distribution for the peripheral compartment.
Survival parameters. λ, base parameter of the Weibull's distribution model in pancreas (λ_p) and ovarian (λ_o) cancer; β, shape parameter of the Weibull's distribution model in pancreas (β_p) and ovarian (β_o) cancer;., parameter that drives the change in hazard elicited by tumour size in pancreas cancer; γ_{TSR}, parameter that drives the change in hazard elicited by tumour size ratio until week 12 or at week 12 for longer times, in ovarian cancer.
Disease–PKPD parameters. TV_0, tumour volume at baseline conditions; K_0, carrying capacity at baseline conditions; λ_1, first-order rate constant that drives tumour proliferation; B, rate constant that controls the stimulatory feedback mechanisms of TV on K dynamics; D, rate constant that controls the negative feedback mechanisms of TV on K dynamics; K_{TR}, first-order rate constant of transfer between transit compartments; $SLOPE_p$, gemcitabine effect parameter in pancreas cancer; Emax, maximum attainable apoptotic effect exerted by gemcitabine in ovarian cancer; CE_{50}, plasma concentration of gemcitabine exerting half of Emax in ovarian cancer; $SLOPE_o$, gemcitabine effect parameter affecting carrying capacity in ovarian cancer; $SLOPE_c$, carboplatin effect parameter affecting carrying capacity in ovarian cancer; IIV, represents the inter-individual variability of the indicated parameter

in the "Published PKPD Models" section. Drug effect parameters were not transformed from those estimated in mice. Values of TV_0 and K_0 were obtained as described in step 2, and the rest of the system-related parameters (first-order rate constants and negative feedback mechanisms) were scaled up to human equivalents (from the estimates listed in Table I obtained in mice) using the following expression (17): $\theta_{human} = \theta_{mice} \times (WGT_{human}/WGT_{mice})^{-0.25}$, where θrepresents

a typical model parameter. Table II shows the resulting values of the system related and the PKPD model parameters used to simulate TV in humans.

TV profiles simulated in mice scale were converted to humans through the ratio between human and mouse body weights and then transformed into size following the expression: $TS = \sqrt[3]{6/\pi \times TV}$.

Using the inter-individual variability (IIV) estimated in the pre-clinical analysis for the system and drug effect parameters, 100 subjects were simulated for each of the cell lines included in the pre-clinical analysis (11): KP4, ASPC1, MIAPACA2, PANC1 (pancreas), A2780, and SKOVxluc3 (ovarian) tumour cell lines. The IIV of TV_0 used for ovarian TGI simulations was set to the IIV estimated in humans (13), due to the absence of such estimate in the pre-clinical PKPD analysis.

Step 4 *Evaluation of the translational approach.* The following two metrics were used to evaluate the performance of the proposed translational framework facilitating the visual comparison between simulated TS and observed TS in patients: (a) Percentage of maximal tumour regression (TR_{max}) occurring at any time during treatment calculated in the case of the pancreatic cancer or (b) ratio between TS at week 12 after the start of the treatment with respect to baseline (TSR_{wk12}), computed in the case of the ovarian cancer. Calculations were performed using the following equations:

$$TR_{max} = \max\left[\left(TS_0 - TS_{(t)}\right)/TS_0\right] \times 100 \quad (4)$$

$$TSR_{wk12} = \left(TS_{wk12} - TS_0\right)/TS_0 \quad (5)$$

Simulations of TS profiles were performed using the R (version 3.2.0) package Simulx (http://simulx.webpopix.org/). Supplementary material 1 presents the R (Simulx) code used to perform these translational TS simulations.

Survival Simulations

In order to support the predictions of the translational TS profiles, OS profiles were simulated using the published models in which either the entire TS profile (in patients with advanced pancreatic cancer) or TS_{Ratio} (in patients with ovarian cancer) was identified as main predictor factors of OS (12,13). The structure of the model for the hazard rate is represented by Eq. (3), and the corresponding parameters are listed in Table I.

For each set of 100 simulated TS profiles, two hundred OS simulations were generated with NONMEM 7.3 (Icon Development Solutions, Ellicott City, MD, USA). The simulated patient population showed the same characteristics as the data used to develop the PKPD models in humans, such as the appearance of new lesions during treatment and the ECOG status measured at baseline (12,13). Simulated OS for each type of cancer was shown as Kaplan–Meier plots and compared with those obtained from clinical data (12,13).

Table II. Parameter Values Used to Simulate TS in Patients

Tumour cell lines	KP4	ASPC1	MIAPACA2	PANC1	A2780	SKOVxluc3_1	SKOVxluc3_2	Parameter definition
Disease progression parameters								
TV_0 (mm^3)	43.59	43.59	43.59	43.59	68.19	68.19	68.19	Tumour volume (TV) at baseline conditions
K_0 (mm^3)	5.6×10^{-3}	22.52	289.22	1.3×10^{-5}	75.2	92.62	51.03	Carrying capacity (K) at baseline conditions
λ_1 (day^{-1})	2.12×10^{-2}	2.6×10^{-2}	4.93×10^{-3}	3.6×10^{-3}	4.9×10^{-2}	5.8×10^{-3}	2.1×10^{-2}	First-order rate constant that drives tumour proliferation
B (day^{-1})	1.11×10^{-1}	4.2×10^{-2}	5.9×10^{-3}	4.4×10^{-2}	6.8×10^{-2}	6.39×10^{-2}	6.39×10^{-2}	Rate constant that controls the stimulatory feedback mechanisms of TV on K dynamics
D (day^{-1} $mm^{3-2/3}$)	1.7×10^{-4}	4.4×10^{-4}	0	0	2×10^{-4}	3×10^{-4}	3×10^{-4}	Rate constant that controls the negative feedback mechanisms of TV on K dynamics
IIV_TV_0 (%)	9	15	44	14	80[a]	80[a]	80[a]	Inter-individual variability of TV_0
IIV_TV_0 (%)	14	29	85	20	–	–	–	Inter-individual variability of K_0
IIV_λ_1 (%)	31	35	79	34	40	51	51	Inter-individual variability of λ_1

[a] IIV_TV_0 set to the IIV estimated in humans (13)

RESULTS

Pancreatic Cancer

The translational modelling approach for gemcitabine in pancreatic cancer was performed for the following four pancreatic cell lines characterized in the mouse xenografts: KP4, ASPC1, MIAPACA2, and PANC1. Table II lists the values of the parameters used to simulate the TS profiles in patients as described in the "METHODS" section. Values of K_0, as seen in the analysis of mice xenografts (11), varied largely across tumour cell lines. Lower K_0 compared to TS_0 induces tumour regression as it was in the case of the KP4 and PANC1 (11). The left panel in Fig. 2 shows that there is an agreement between TS observed in patients (12) and the simulated obtained based on the proposed translational framework. Remarkably, the agreement is higher for the case of the PANC1 cell line based on a visual assessment. It is also worth noting that variability is greater in the patients than in the simulated individuals generated using human typical population PK parameters and mouse-derived PD parameters. In the upper panels of Fig. 3, simulated time profiles are shown for each cell line separately.

ASPC1 and, especially, KP4 cell lines appear to be the most sensitive at early times after the initiation of the treatment, showing faster subsequent disease progression. PANC1 appears to be the most sensitive cell lines during the whole treatment period, while MIAPACA2 appears to be the least. In addition, it stands out the differences between the TS profiles shown by KP4, ASPC1, and MIAPACA2 cell lines and by patient's observed data at late times. This discrepancy could be justified by the fact that translational simulations ignored drop outs.

The simulated profiles shown in Fig. 2 (left) and Fig. 3 (upper) were translated into the clinical context calculating different metrics of tumour regression. In Fig. 4, TR_{max} showed median values of 10% (pooling all cell lines together), 17% (KP4), 5% (ASPC1), 0% (MIAPACA2), and 14% (PANC1) that are within the range of values predicted with the PKPD model developed with the clinical data (4%).

Finally, in Fig. 5 (left panel), the results corresponding to OS are shown. Simulations obtained pooling together the simulated TS profiles from the four cell lines studied in xenografts adequately described clinical observed data.

Ovarian Cancer

Taking into account that during the pre-clinical analysis, TV_0 and rate of proliferation exhibited inter-study variability in the case of the SKOVxluc3 cell line (11), two different sets of simulations were performed for this cell line. The reported K_0 values show much more consistency across cell lines, which, in the case of pancreas cancer, range from 68.2 to 92.6 mm^3. The right panel in Fig. 2 shows that there is a good agreement between tumour observed data in patients (13) and the simulated profile. As occurred in pancreatic cancer, variability is greater in patients that in simulated individuals using human population typical PK parameters and mouse-derived PD parameters. In the lower panels of Fig. 3, simulations are shown for each cell line separately. The cell line A2780 appears to be the most sensitive during the whole treatment period in comparison with the SKOVxluc3 cell line. The simulation results shown in Figs. 2 and 3 indicate that treatment effects on tumour shrinkage are more pronounced in ovarian cancer than in pancreatic cancer.

In Fig. 4, TSR_{wk12} showed median values of −0.6 (pooling together cell lines), −0.6 (SKOVxluc3_1), −0.45 (SKOVxluc3_2), and −0.9 (A2780) that are within the range of values predicted with the PKPD model developed with the clinical data (−0.5).

Figure 5 (right panel) shows similar OS results to those obtained in the pancreatic cancer, where simulations for the ovarian cell lines described the clinical outcome during the treatment period quite well.

DISCUSSION

In this retrospective analysis, the model-informed Drug Discovery and Development (MID3) paradigm has been successfully applied to gemcitabine data linking pre-clinical and clinical responses through a mechanistic translational

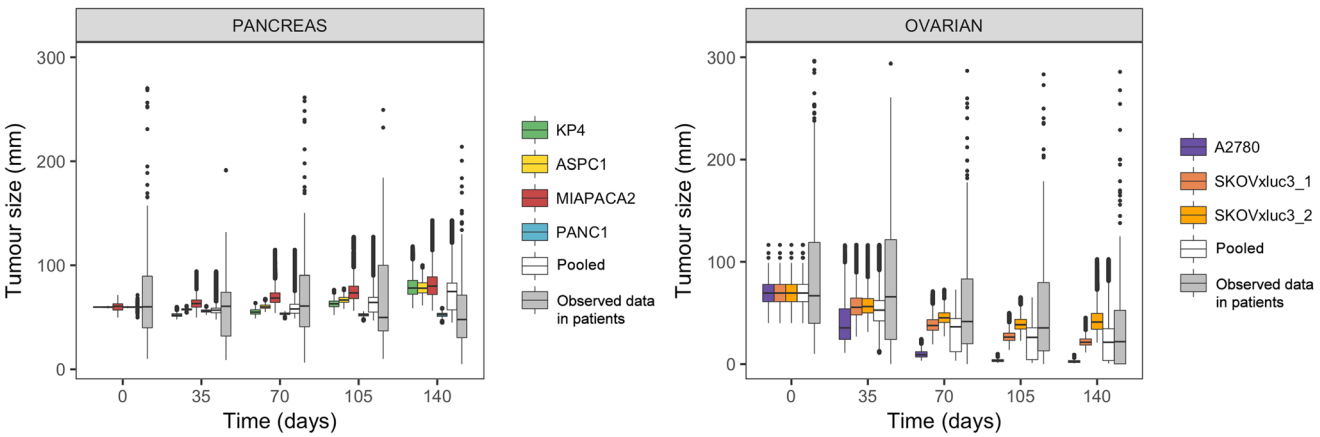

Fig. 2. Boxplots of TS simulations over time performed for pancreas (left panel) and ovarian (right panel) cancer. Time was binned each 35 days, creating 5 time intervals on which the distribution of TS is displayed. "Pooled" label includes the simulations obtained from all cell lines together, for both pancreas and ovarian. The number of original TS observations in patients was 752 in pancreas (12) and 2693 (13) in ovarian. The height of each box covers the interquartile range, and the horizontal line represents the median of the distribution. Dots represent outliers

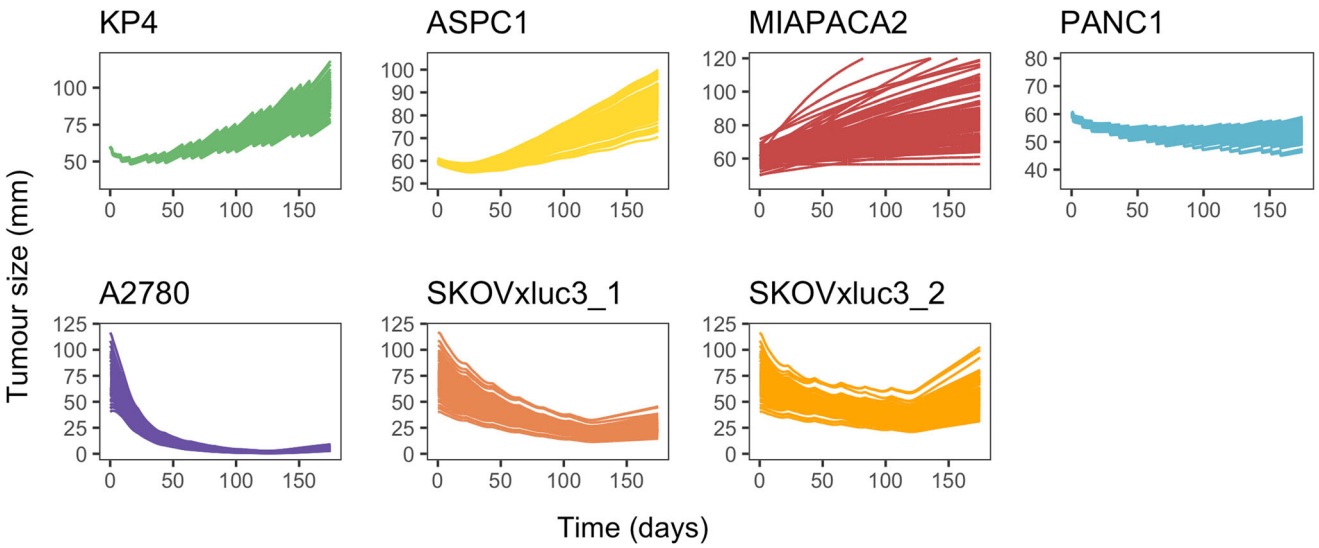

Fig. 3. TS simulated profiles for each pancreatic (top panels) and ovarian (bottom panels) cell line

model-based approach. The methodology proposed, which couples pre-clinical PKPD model, clinical PK models, and dosing schedules, together with an allometry-based mouse-human conversion, was able to provide a good description of tumour response and survival data for patients with pancreatic and ovarian cancer treated with gemcitabine alone or in combination with carboplatin. The purpose of this study was to develop a pharmacometric-based framework which would help predict drug efficacy in humans from early development phases, thus assisting and optimizing the drug development and discovery process in oncology.

The results obtained from the current analysis provide further support for the use of mouse xenograft experiments, despite the long discussion and controversy surrounding their predictive capacity (6,18), and show that they provide a wealth of information regarding tumour behaviour and drug effects. Moreover, the development of such translational approaches may assist in the design of pre-clinical analyses and selection of predictive xenograft cell lines, with the aim of optimizing translation to the clinic. As an example, Spilker and colleagues (19) have recently highlighted the importance of identifying and selecting non-clinical doses to be used in mouse experiments that reflect clinical drug concentrations. This allows the efficacy of newly developed drugs to be compared against standards of care at concentrations which can be safely achieved in the clinic.

Similarly, Lindauer and colleagues (20) have developed a semi-mechanistic model, including information regarding

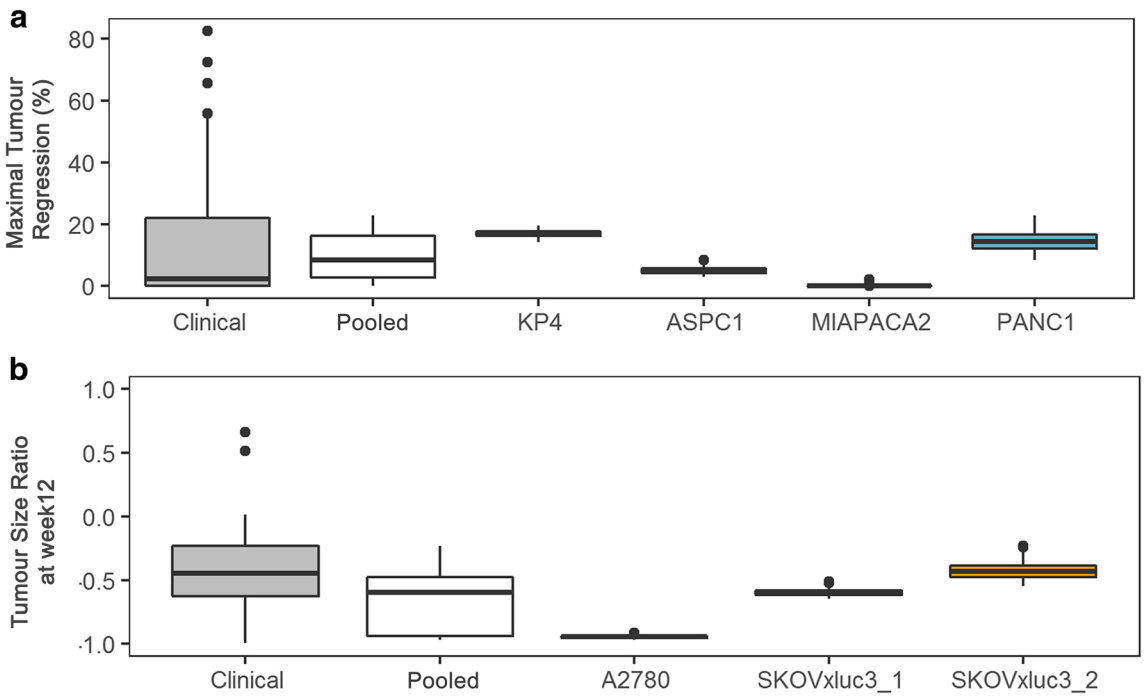

Fig. 4. Boxplots of **a** maximal tumour regression (%) obtained for pancreas cancer and **b** tumour size ratio at week 12 for ovarian cancer

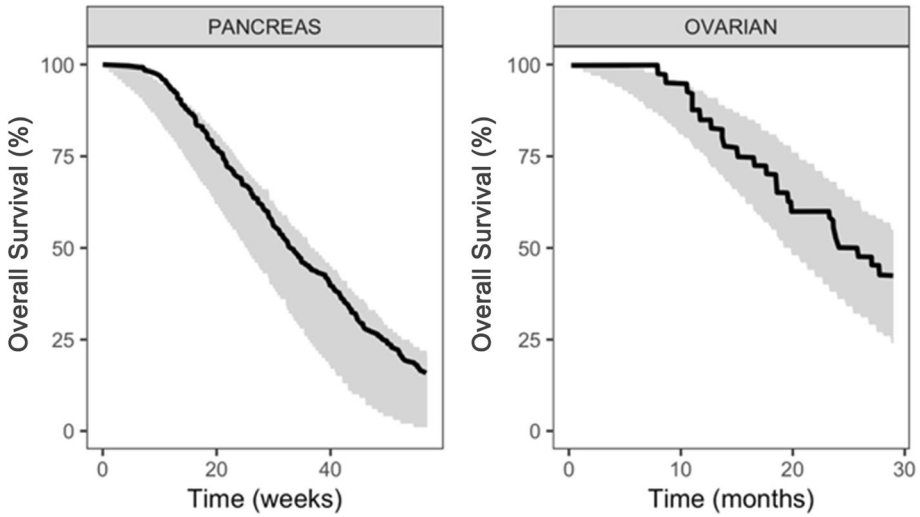

Fig. 5. Overall survival probability over time: pancreas (left panel) and ovarian cancer (right panel). Continuous black line represent the Kaplan–Meier plot corresponding to patient data (285 patients in pancreas and 44 in ovarian) (12,13). The grey-shaded area represents the 95% prediction interval of the simulated overall survival probability based on the proposed translational approach, pooling for each type of cancer all cell lines

receptor-binding characteristics, obtained from pre-clinical experiments, in order to assist with dosing selection during the clinical development of the anti-body Pembrolizumab. We are aware of the differences regarding the immune system between animals and humans; however, from our perspective, the key point is to invest resources in developing mechanistic models in the pre-clinical arena, which is supported by the current work. In this regard, Ouerdani *et al.* (21) have recently shown that the structure of models developed using xenograft data can be translated to the analysis of TS human data. The work proposed in our analysis is a good example of a model-based framework that goes beyond the single mechanism-based models, providing the flexibility required to incorporate the effect of different classes of anti-cancer drugs (as it is shown in the case of gemcitabine–carboplatin combination in ovarian cancer).

In line with this, the development of pre-clinical semi-mechanistic PKPD models that differentiate between system and drug-related parameters is crucial for translational research (22), due to the fact that drug-specific PD parameters are likely to be similar across species (23), and therefore, extrapolation might not be required. In contrast, system-specific parameters (in this case, TS_0, K_0, and proliferation rate constants) should be adapted to each tumour type and species. The approach used in the current analysis for rescaling system-related rate constants from mouse to human has already been applied in non-small cell lung cancer (17) and for describing cancer progression in an allometric PKPD model developed for a novel IGF-1 receptor inhibitor (24). Recently, in the work by Zhu and colleagues (25), gemcitabine effects were scaled from proteomics to cell culture and then to human response, opening an avenue to integrate tumour size within a more mechanistic approach increasing its predictive performance as surrogate endpoint.

Pre-clinical modelling has been applied in drug research for making go/no go decisions (26,27). However, even when pre-clinical quantitative analyses are performed, most decisions are usually made according to qualitative relationships (i.e., treated/control tumour weight ratio = 40% (18)).

The use of modelling and simulation in translational oncology focusing on the use of tumour growth dynamics measured in xenograft studies has been explored before (8,19,24). The current study presents both similarities and differences with respect to previous reports in relation to: (a) drugs and data for which the approaches were developed; (b) mouse–human scaling methodology; (c) doses used for performing the simulations; (d) comparison with clinical data; and (e) conclusions and contributions to translational research.

Particularly noteworthy is the use of already marketed drug information that allows a successful comparison between the outcome of translational-based simulations and the clinical outcome to be established (8,19). In the previous studies, differences in system parameters across species were not taken into consideration, and TGI profiles were simulated during the first cycle of the chemotherapy cycle, without considering disease progression or delay in drug response. However, Titze and colleagues (24) considered differences in system parameters for the different species and successfully applied their translational approach, predicting the optimal dose that would produce the maximum effect with minimum side effects. Unfortunately, the lack of clinical data so far makes it impossible to validate their approach.

In our analysis, different degree of response to treatment (mainly in the pancreas case study) was identified from the results of the translational TS simulations between cell lines. This situation is also observed in the clinical scenario, where tumour proliferation and drug effects on patients with advanced pancreatic cancer are associated with a high variability (12). In this context, it can be proposed that genetic factors associated with each cell line, affecting, among other processes, tumour proliferation and the gemcitabine metabolism pathway, could be responsible for the different tumour behaviour and response to treatment (28,29).

It is noteworthy that the variability observed in the clinical observations regarding tumour response is significantly higher than that predicted from the translational simulations. Nevertheless, the methodology proposed does not aim to predict individual data but to anticipate overall response. In this line, our results encourage the use of multiple cell lines in the pre-clinical setting to stratify them, in terms of growth rate and drug sensitivity anticipating variability in drug response and overall efficacy within the patient population. Similar results have been described by Parra-Guillen *et al.* (30) which suggest that, due to the high variability of tumour proliferation across different cell lines, the analysis of multiple cell lines should be considered in the translation of drug efficacy information to the clinical scenario.

One limitation in the context of pre-clinical compound selection is the requirement of PK models based on patient data, in order to perform the simulation exercises, which in principle implies that the drug has to be already administered to patients. One possibility to overcome such limitation which has not been addressed in the current work might be to develop a physiological-based PK model allowing a mechanistic scaled-up of animal to human drug exposure (31,32). Another limitation comes from the fact that the current framework is based on a semi-mechanistic PKPD model (see Fig. 1b) (11); however, the model lacks interaction between gemcitabine and carboplatin as the effects are incorporated in an additive form.

CONCLUSIONS

To conclude, while not the first example of translational tumour response from mice to humans, the current analysis adds important contributions to the drug development and discovery process, being, one of the first translational approaches providing the framework required to incorporate the effect of different classes of anti-cancer drugs.

ACKNOWLEDGEMENTS

Support was received from the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115156, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and the EFPIA companies' in kind contribution. The DDMoRe project is also financially supported by contributions from the Academic and SME partners.

At the time the research was performed, Iñaki F Troconiz was an employee of the University of Navarra and Maria Garcia-Cremades was a PhD student from the University of Navarra. Celine Pitou and Philip W Iversen were employees of Elli Lilly and Company.

The authors would like to thank Sonya Tate for providing assistance during the writing process.

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