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Data analysis and model evaluation of chemotherapy induced neutropenia
Results from the PARTNER trial

David Hodson[1], Claire Villette[1], Lea Sta[1]., Mila Roca[2], Megan Rowley[2], Joni Howells[2], Christophe Chassagnole[1], Joanna Gale[2].

[1]Physiomics plc, Milton Park, OX14 4SB, UK. [2]Portsmouth University Hospitals NHS Trust, Oncology, Portsmouth, UK

Tel. +44 (0) 1235 841575. Email: lsta@physiomics.co.uk

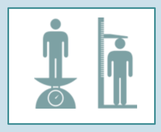
Introduction

- Docetaxel (DOC) is often used to treat advanced prostate cancer (PC)[1].
- Neutropenia is one of the main risks for patients undergoing DOC treatment.
- Physiomics have developed a prototype precision dosing tool based on a PK/PD model of myelosuppression for DOC in PC[2,3] with the aim of reducing toxicity.
- An NIHR i4i award (NIHR201282) funded an observational clinical study (PARTNER - NCT04823910) to evaluate the tool against clinical data collected on PC patients treated with DOC.
- Granulocyte Colony Stimulating Factor (G-CSF) is often co-administered with DOC prophylactically to mitigate the risk of neutropenia[1,4,5] and thus needs to be accounted for in the precision dosing tool.
- The model of myelosuppression was extended to add the impact of G-CSF co-administration on neutrophil profiles. A secondary aim of this research was to validate this extended model.

Clinical question in a nutshell

+50k — Prostate cancer diagnoses each year in the UK

Docetaxel as chemotherapy in advanced stage



Docetaxel dose commonly guided by BSA

3 weeks — Cycle length for docetaxel treatment

Main docetaxel toxicity is neutropenia

20 % — Patients may be overdosed[1]

30 % — Patients may be underdosed[2,4,5]

[1] Kryzanski, W. et al. (2010). Journal of clinical pharmacology. 50(9 Suppl):101S-112S
[2] Villette, C.C. et al. (2023). Front. Oncol. 13:1154493.
[3] Hurry C, et al (2021). Cancer Res, 81 (13_Supplement):228–8.
[4] Gurney, H. (2002). British journal of cancer, 86(8), 1297.
[5] Engels, F.K. et al. (2011). Clinical Cancer Research, 17(2), 353-362.

Methods

- The study comprised a total of 31 patients split between DOC treated (n=17) and DOC+G-CSF treated cohorts (n=14) (Figure 1). Patient demographics were also collected (Table 1).
- The core myelosuppression model, docetaxel PK and G-CSF PK were adapted from the literature[1,6,7,8], with the exception that feedback from circulating neutrophils on progenitor proliferation was explicitly mediated by endogenous G-CSF (Figure 2).
- Docetaxel plasma concentrations were collected at two time-points on the initial visit (Figure 3). Patient neutrophil profiles were collected weekly for two 3-weekly cycles of docetaxel (Figure 4 & 5).
- All parameters controlling the impact of G-CSF were calibrated using clinical data available in the literature. The baseline absolute neutrophil count ('ANC') level was fixed to the initial ANC value for each patient. Three patient-specific parameters were fitted using Bayesian post-hoc analysis in nlmixr; Edrug – describing the docetaxel mediated inhibition rate of neutrophil proliferation, MTT – describing the mean transit time taken for a neutrophil progenitor cell to develop into a mature neutrophil, and γ which represented neutrophil mediated negative feedback of endogenous G-CSF production.
- Inter-individual variability was assumed to be log-normally distributed. Model estimation error from cycle 1 (fit) was calculated using the goodness of fit error. Model estimation error from cycle 2 (prediction) was calculated using the root-mean square error (RMSE).

[6] Friberg, L.E. et al. (2002). Journal of clinical oncology, 20(24), 4713-4721.
[7] McLeod, H.L., et al. (1998.). Cancer chemotherapy and pharmacology, 42(2),155-159.
[8] Quartino, A. et al. (2012). Pharmaceutical research, 31(12). 3390-3403

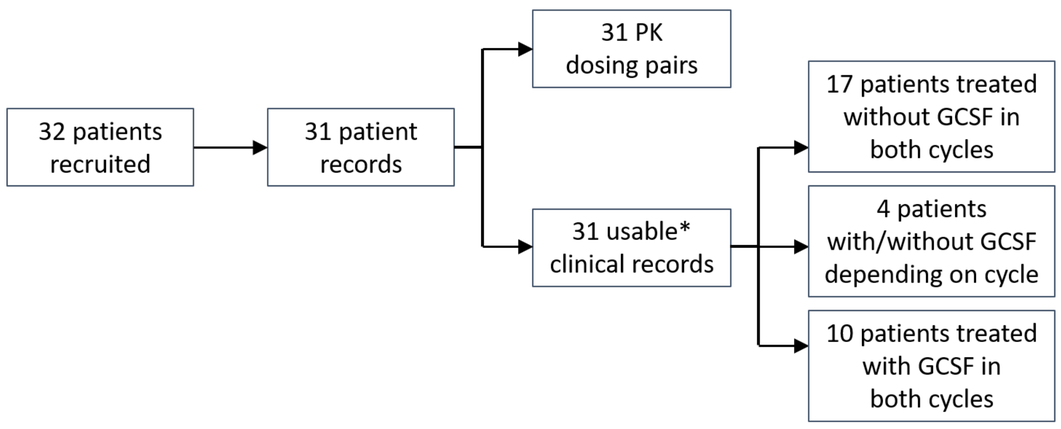


Fig 1: Schematic of data recorded as part of the PARTNER trial (*usable clinical records refer to records containing at least the first administered dose of docetaxel and the ANC counts at baseline (<= day 0), close-to-nadir (~day 7), and during recovery (~day 14) of the first cycle).

	Count	Min	Max	Mean	Median	StDev
Age (y)	31	54	82	68.97	71	7.26
Height (m)	31	1.64	1.87	1.75	1.77	0.06
Weight (kg)	31	62.95	111.15	87.19	87.9	13.65
BMI (kg/m²)	31	20.23	34.57	28.33	28.8	4.07
BSA (m²)	31	1.69	2.32	2.03	2.04	0.16
ECOG perf. status	31	2	2	2	2	0

Table 1: Summary of Patient Demographics

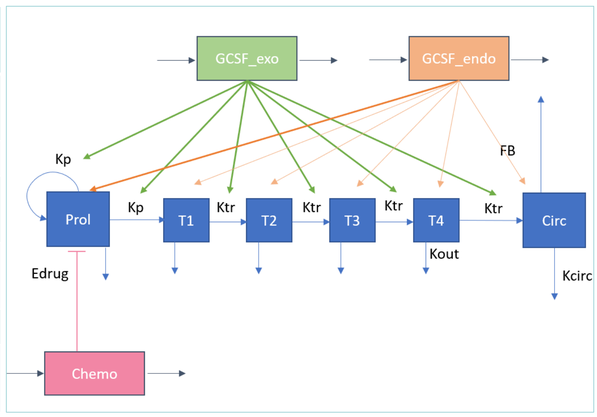


Fig 2: Schematic of the extended model fitted to patients treated with DOC alone or DOC+ G-CSF.

Results

- Individual patient docetaxel PK profiles (Figure 3) indicated that most patients exhibited PK profiles within the 95% prediction interval (PI) of the PK model described in [7], confirming the validity of the model for use in the PK/PD model.
- ANC profiles predicted by patient-specific models for patients not co-treated with G-CSF are displayed in Figure 4. The patient-specific model fitting procedure converged for 15 of 17 patients not co-treated with G-CSF. Individual fits indicated that the model sufficiently captured the neutrophil profiles, particularly at the 7 day timepoint, which is the point most reflective of the nadir in the observed data.
- ANC profiles predicted by patient-specific models for patient co-treated with G-CSF are displayed in Figure 5. The patient-specific model fitting procedure converged for 12 of 14 patients co-treated with G-CSF.
- The extended model captures shortening of neutropenia due to G-CSF. However, overall fits (exact values and timings) remain poorer than for docetaxel treatment alone.

PK/PD model validation

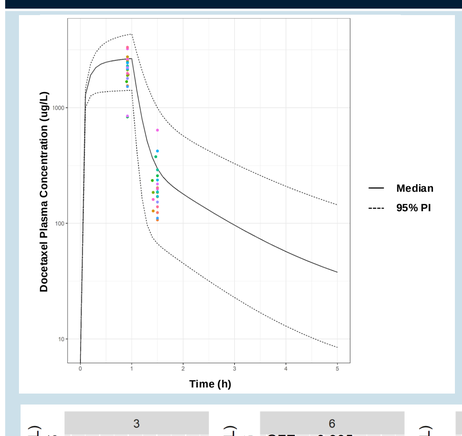


Fig 3: Docetaxel concentration measured in patients treated with docetaxel at 75 mg/m² in 1h infusion (colour dots) overlaid on McLeod's predicted median (plain line) and 2.5/97.5 percentiles (dotted lines) indicate reasonable concordance of the observed data to the model described in [7].

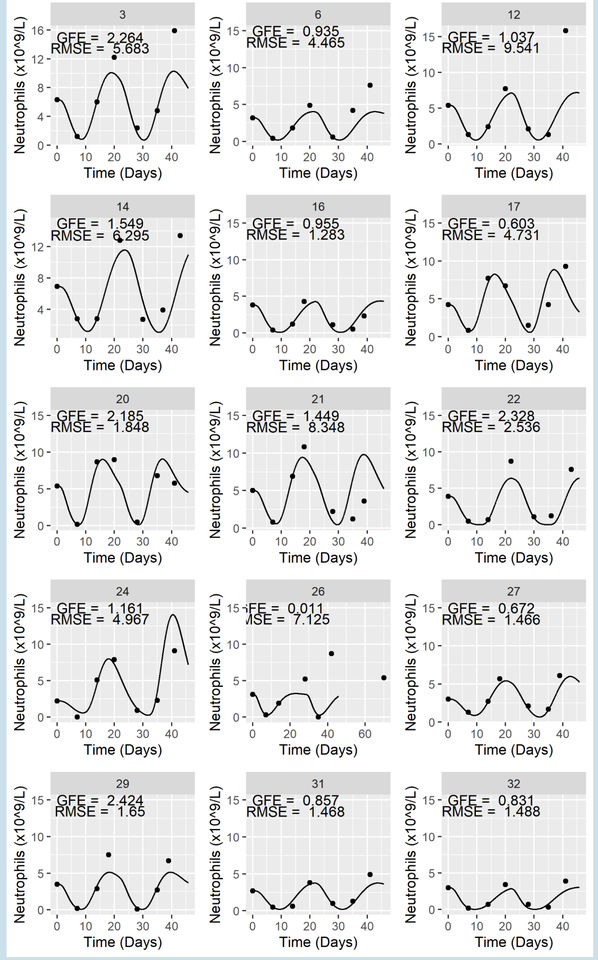


Fig 4: Predicted DOC-treated patient specific ANC profile model prediction (line) overlaid on clinical data (dots) indicate reasonable concordance of the data with the model outlined in Fig 2. GFE= goodness of fit error (1st cycle). RMSE= root mean square error on predictions (2nd cycle).

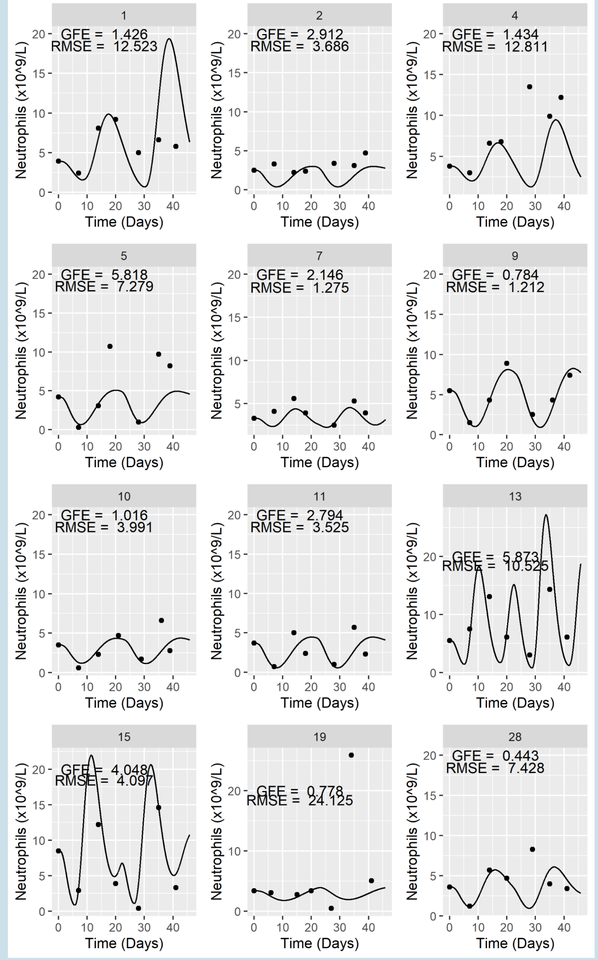


Fig 5: Predicted DOC+G-CSF-treated patient specific ANC profile model prediction (line) overlaid on clinical data (dots) indicates that further model refinement or data collection is needed to accurately capture ANC profiles of G-CSF treated patients.

Conclusions and future perspectives

- The initial model fitted the individual neutrophil profiles of patients treated with DOC alone and showed reliable precision and low degrees of error.
- The extended model captured shortening of neutropenia due to G-CSF co-medication. It also captured a general trend in lesser severity and earlier occurrence of nadir compared to DOC treatment alone.
- Prediction of precise ANC levels and timing of G-CSF administration require model refinement, warranting further study and additional clinical data.
- We hypothesise that additional clinical data collected during the nadir (Days 10-12) would further enable more precise model fitting to G-CSF treated patients.
- Physiomics are currently setting up a clinical trial in collaboration with Blackpool Teaching Hospitals NHS Foundation Trust, part-funded by Innovate UK award (#10086568: Predict-Onc), which will aim to capture neutrophil profiles including additional timepoints, the resulting data will be fit to the model described above to validate this hypothesis.