A precision dosing application for patients treated with docetaxel and G-CSF

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Introduction

The aim of this work was to produce a precision dosing application for clinicians to control neutropenia in patients treated with both docetaxel and G-CSF.

Chemotherapy induced neutropenia (CIN) poses serious harm to patients due to the heightened risk of severe infection. Accordingly, chemotherapy dose is assessed at the beginning of each cycle. The therapeutic window of chemotherapy is determined from population studies, with an individual's dose often scaled by their body surface area. This leads to a large number of patients being over- or under- dosed. We previously developed an application [1] which uses weekly neutrophil counts from the first cycle of docetaxel treatment to predict the level of neutropoenia in subsequent cycles for a given dose of docetaxel. However, in the original app the administration of G-CSF, used as a prophylactic treatment for neutropenia, was not considered. G-CSF administration lacks standardisation and the COVID-19 pandemic has created a highly risk averse environment to infections, raising the prospects that a clinician will administer G-CSF.

[1] Villettte C., et al., Proceedings of the AACR Annual Meeting 2019; 2019 Mar 29-Apr 3; Atlanta, GA. Philadelphia (PA): AACR; Cancer Res 2019;79(13 Suppl):Abstract nr 677.

Clinical question in a nutshell

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

Docetaxel as chemotherapy in advanced stage

Docetaxel dose commonly guided by BSA

20 % — Patients may be overdosed

30 % — Patients may be underdosed

Main docetaxel toxicity is neutropenia

G-CSF — Commonly used to control neutropenia

Methods

We adapted representations of endogenous and exogenous G-CSF action on CIN from the literature [2,3,4] to capture the inherent feedback effect of circulating neutrophils on progenitor proliferation as well as the stimulatory action of G-CSF on proliferation and maturation of progenitor cells (Fig 1).

Using data in the public domain from the comparator arm of a phase III clinical trial for metastatic hormone-resistant prostate cancer (NCT00617669), we identified 134 patients treated with docetaxel with recorded weekly blood tests in the first and second cycle, including 27 also receiving G-CSF (pegfilgrastim and filgrastim). We tested the ability of the model structure to capture individual neutrophil profiles using variable parameter calibrations.

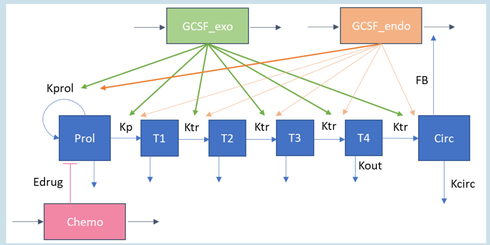

Fig 1: Schematic of the combined myelosuppression model

We also tested this model in a different setting, by calibrating it to capture the mean neutrophil profile from two arms of a clinical trial [5] comparing chemo alone and filgrastim + chemo. In this trial, neutrophil counts were measured daily.

[2] Friberg, L.E., et al., 2002. J. Clin. Onc., 20(24). [3] Quartino, A.L et al., 2014. Pharm. Res, 31(12). [4] Krzyzanski, W., et al. 2010. J. Clin. Pharmacol, 50(S9). [5] Crawford, J., et al. 1991. N. Engl. J. Med, 325(3)

Role of the App within the standard of care pathway

Figure 2 illustrates how the App fits within the current standard of care pathway.

- In the current standard of care, the first docetaxel dose is selected based on patient BSA. A blood sample is routinely collected on the day of first injection and sometimes on the first day of each subsequent cycle. If clinical toxicity is observed, the next dose is reduced and/or accompanied by G-CSF, or the treatment is terminated. Docetaxel is administered in 3 week cycles until switch to another line of treatment, unacceptable toxicity or death.
- Our precision dosing App requires two additional blood tests during the first chemotherapy cycle around day 7 and day 14.
- Just before selecting the second chemotherapy dose, patient characteristics (age, height, weight) and blood tests results are entered into the App which outputs an evaluation of neutropenia in the past cycle as well as a prediction for the next cycle. Simulations of dose changes can be run in seconds.
- Toxicity information provided by the App may help clinicians to identify effective, under or overdosing and modulate the docetaxel dose and G-CSF co-medication accordingly.

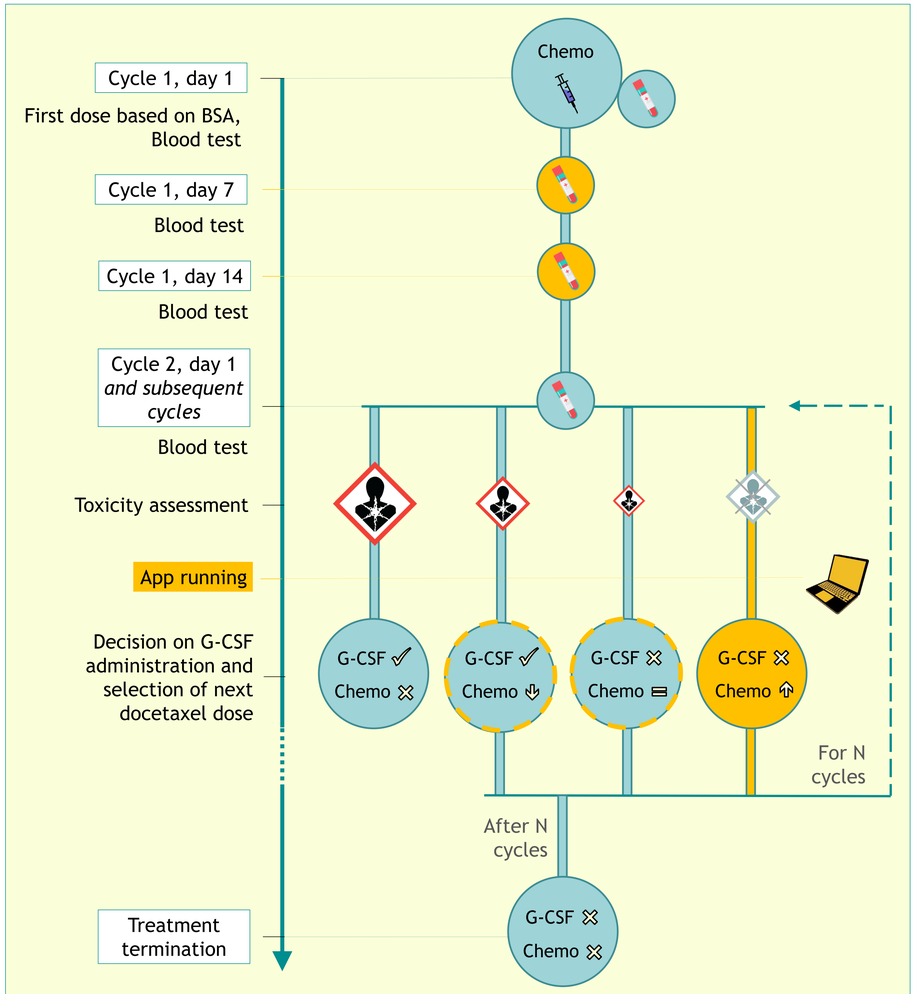

Fig 2: Schematic of the role of the App (yellow) within the standard of care pathway (green).

Main results

- The combined myelosuppression model was successfully calibrated to capture individual neutrophil profiles for patients receiving docetaxel chemotherapy (Fig 3). Captured features include apparent chemotherapy-induced nadir, rate of recovery, and subsequent overshoot over baseline.
- The combined model captured earlier recovery and increased neutrophil levels following pegfilgrastim and filgrastim administration (Figs 3-4), as well as earlier and less severe nadir (Fig 4).
- The model correctly predicted neutrophil peaks at the start and end of consecutive filgrastim administration, although their amplitude was underestimated (Fig 4).

Illustrative cases

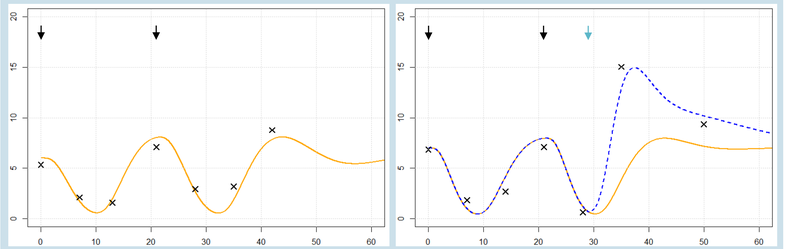

Fig 3: Simulated patient-specific neutrophil profiles (ANC, billion/L) over time (days) overlaid on clinical measurements (black crosses). Left: patient on docetaxel 75mg/m^2 (black arrows). Right: patient on docetaxel 75mg/m^2 and pegfilgrastim 6mg (blue arrow). Simulations with and without G-CSF consideration displayed in blue and orange, respectively.

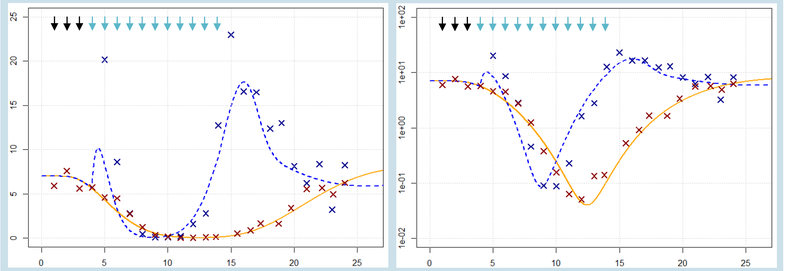

Fig 4: Simulated neutrophil profiles (ANC, billion/L) over time (days) under chemotherapy alone (orange) or chemotherapy + filgrastim (blue), overlaid on the mean clinical measurements. Left: linear y scale. Right: log y scale. Chemo (black arrows) and filgrastim (blue arrows) were administered as per trial protocol [5]. Chemo involved cyclophosphamide 1000mg/m^2 and doxorubicin 50mg/m^2 on day 1, and etoposide 120mg/m^2 on days 1 to 3.

Conclusion

The model was able to capture the main features of endogenous and exogenous G-CSF action on neutrophil count described in the literature, including endogenous-G-CSF-mediated rebound above baseline after chemotherapy-induced depletion [2], rapid rise in neutrophil count following exogenous G-CSF administration [5], as well as reduced chemotherapy-induced depletion and earlier recovery under G-CSF treatment compared to chemotherapy alone. Next steps involve deriving the corresponding population model able to described inter-patient variability in chemotherapy-induced neutropenia and G-CSF action.