A Precision Dosing Application For Advanced Prostate Cancer Chemotherapy

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Introduction

The therapeutic window of chemotherapy drugs is commonly established at a population level and patient dose selection is often simply scaled with Body Surface Area (BSA). Due to large inter-individual physiological variability, this leads to a significant number of patients being under or over-dosed [1,2]. While a limited number of precision dosing techniques exist to tailor patient-specific treatment, they typically require costly additional tests which severely restrict their use in clinical practice.

Focusing on docetaxel for advanced prostate cancer, we have developed a demonstrator for precision dosing which requires a single weekly classical blood test in the first chemotherapy cycle. It will fit within the current clinical practice to improve patient outcome at low cost.

[1] Gurney, H. (2002). British journal of cancer, 86(8), 1297.
[2] Engels, F.K. et al. (2011). Clinical Cancer Research, 17(2), 353-362.

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

3 weeks — Cycle length for docetaxel treatment

Main docetaxel toxicity is neutropenia

20 % — Patients may be overdosed [1]

30 % — Patients may be underdosed [2]

Methods

- The demonstrator App was developed using publicly available data from the comparator arm of a phase III clinical trial for metastatic hormone-resistant prostate cancer (clinical trial number NCT00617669 [3]). This cohort includes 412 patients who were treated with docetaxel between 2008 and 2011 in cycles of 3 weeks with weekly blood tests in the first cycle.
- A population PK/PD model for docetaxel and neutrophil population was assembled based on the literature [4, 5].

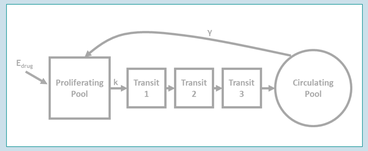

Fig 1: PD model [4]

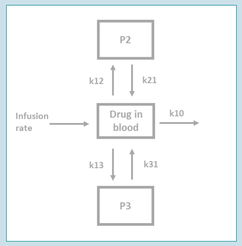

Fig 2: PK model [5]

- Individual patient PK/PD parameters including docetaxel clearance were estimated by calibrating the population model with weekly measured blood count using a combination of Bayesian and machine learning approaches.
- Cox models were developed using estimated patient PK/PD parameters which relate docetaxel exposure and biomarker levels to overall and progression free survival.

[3] Fizazi, K. et al. (2013). Journal of Clinical Oncology, 31.14, 1740-1747
[4] Friberg, L.E. et al. (2002). Journal of clinical oncology, 20(24), 4713-4721.
[5] McLeod, H.L., et al. (1998.). Cancer chemotherapy and pharmacology, 42(2),155-159.

Role of the App within the standard of care pathway

Figure 3 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 or the treatment 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 and patient median survival probability relative to the general population under the current dose (Figures 4 and 5). 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 dose accordingly.

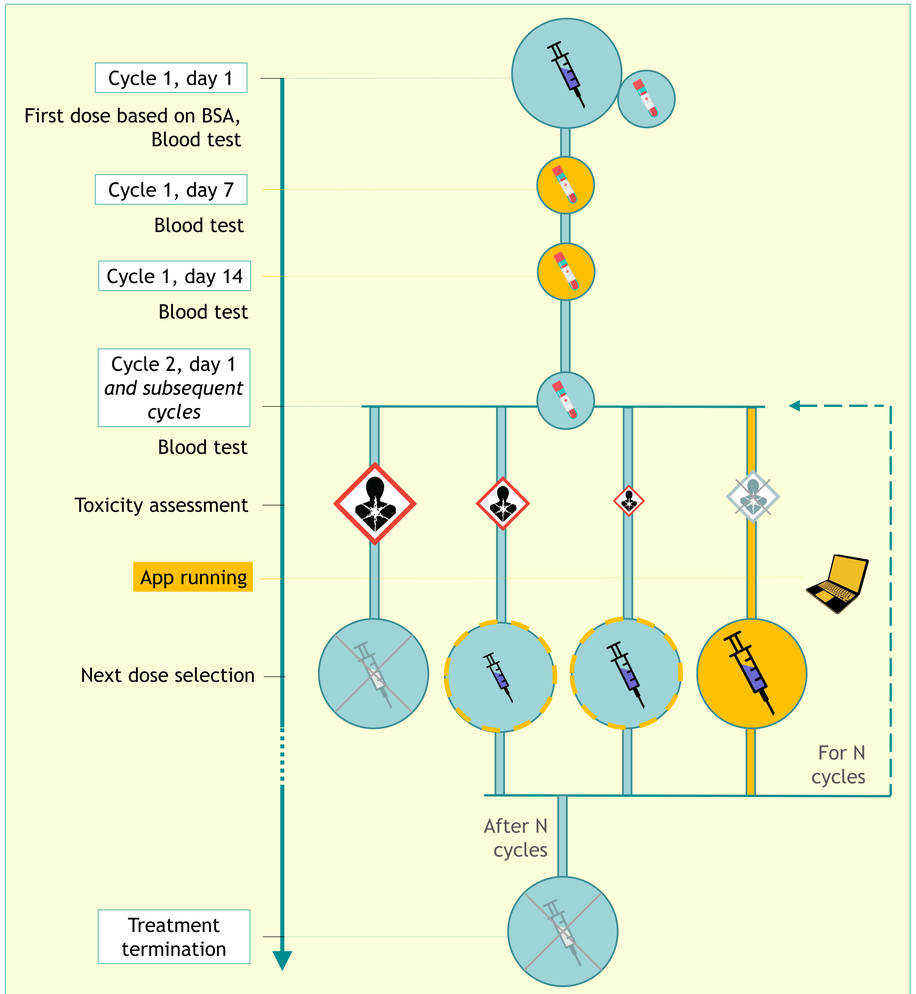

Fig 3: Schematic of the role of the App (yellow) within the standard of care pathway (green).

Results

- Concordance levels of 0.69 and 0.6 were obtained for the overall and progression-free survival models, respectively.
- Significant predictive variables include docetaxel exposure, Prostate Specific Antigen (PSA) as well as other biochemical markers.
- Patients with low estimated hematologic toxicity (neutrophil count not dropping under 0.5 billion/L) presented a median overall survival time of 480 days, against 625 days for patients with higher hematologic toxicity.
- Patients with low estimated docetaxel exposure (<3 µg.h/mL) presented a median overall survival time of 450 days, against 580 days for patients with higher estimated docetaxel exposure.

Illustrative underdosing case

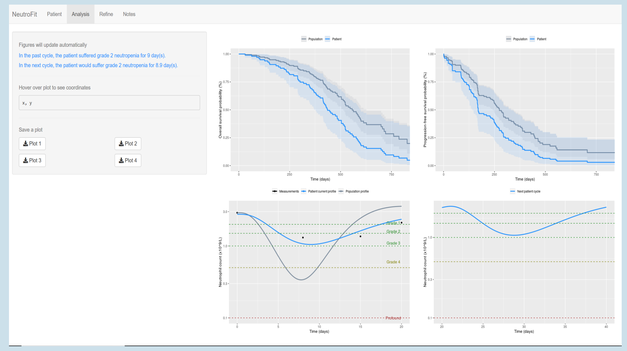

Fig 4: Screenshot of the App 'analysis' tab. Overall and progression free survival models (top), neutropenia model for last (left) and upcoming (right) cycles. Patient models (blue) are compared to population models (grey) for administered 75mg/m² dose.

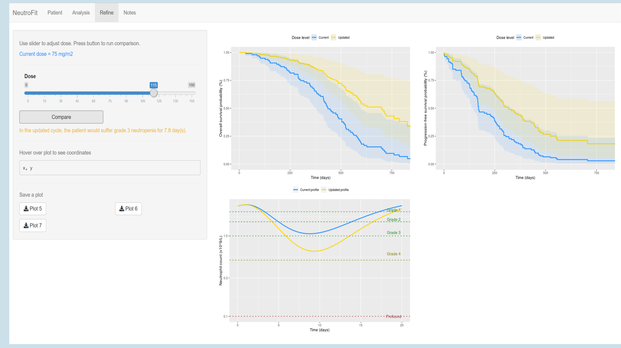

Fig 5: Screenshot of the App 'dose refinement' tab. Simulation of survival probability and neutropenia in upcoming cycle for current (blue) and increased dose of 115 mg/m² (yellow). Estimated increase in median overall survival time from 440 days to 650 days.

Conclusion

We have developed a precision dosing App for Docetaxel in advanced prostate cancer which requires a single weekly standard blood test in the first chemotherapy cycle. Next stages include a validation clinical trial. This App has the potential, if approved by regulators, to significantly improve patient outcome and toxicity risk at low cost without disrupting the clinical treatment pathway.