

Importance of Quantifying Neutropenia Risk Factors in Phase I Solid Malignancy Dose Finding; A Simulation Case

Alienor Berges¹, Martin Johnson¹ and Alexander MacDonald¹

¹Clinical Pharmacology, ADME and AI, Clinical Pharmacology & Safety Sciences, R&D BioPharmaceuticals, AstraZeneca, Cambridge, UK

Background & Work Objective

- In oncology, the primary objective of most oncology phase I studies is to identify the **Maximum Tolerated Dose (MTD)**
A dose/regimen found to have limited dose-limiting toxicities (DLT), in a small group of patients (typically ≤ 1 out of 6), over a finite period of time (usually 21-28 days following treatment).
- Scientific and statistical limitations of this approach are well-documented [1]. However, patient characteristics may influence the MTD identified in these studies.
- We have previously reviewed the risk factors for neutrophil toxicity in cancer populations [2], and Lyman *et al.* have quantified risk of neutropenic complications in patients undergoing chemotherapy [3].

We present a simulation study to assess the effect of various patient's risk to dose-limiting neutropenic complications (represented by severe or febrile neutropenia (SN/FB)) on the MTD of a theoretical anti-cancer agent.

Methods

1. Logistic regression risk model from Lyman^[3]

- Includes i) background risk α , ii) patient's risk prior to treatment, based on the patient's specific risk factors X_m and their associated effect $\beta_{i,m}$ and iii) dose-related drug effect toxicity.

$$\text{Logit}(p_{SN/FB}) = \alpha + \beta_{i,1} \times X_1 + \beta_{i,m} \times X_m + C_{\text{DRUG}} \times \text{DOSE}$$

where i is the subject index and m the covariate index
 $\beta_{i,m} \sim N(\mu, \sigma^2)$ with μ and σ^2 derived from Lyman's model
 C_{DRUG} is a fixed typical value (no patient variability)

- Binary individual SN/FB events (1 if presence or 0 if absence) are generated according to a binomial distribution given $p_{SN/FB}$ and a sample size per group.

2. Simulations

- Settings are typical of a dose escalation study, with 5 doses [0.1, 1, 3, 6 & 9 mg] and 6 patients per dose level.
- 4 scenarios were selected (Table 1)

Table 1. Four scenarios based on drug toxicity and on patient's risk prior to treatment

	Low Drug Toxicity	High Drug Toxicity
Low Risk Population	Highest dose lead to $p_{SN/FB} = 0.5$ Baseline Risk factors leads to $p_{SN/FB} = 0.05$	Highest dose leads to $p_{SN/FB} = 0.9$ Baseline Risk factors lead to $p_{SN/FB} = 0.05$
High Risk Population	Highest dose lead to $p_{SN/FB} = 0.5$ Baseline Risk factors leads to $p_{SN/FB} = 0.2$	Highest dose lead to $p_{SN/FB} = 0.9$ Baseline Risk factors leads to $p_{SN/FB} = 0.2$

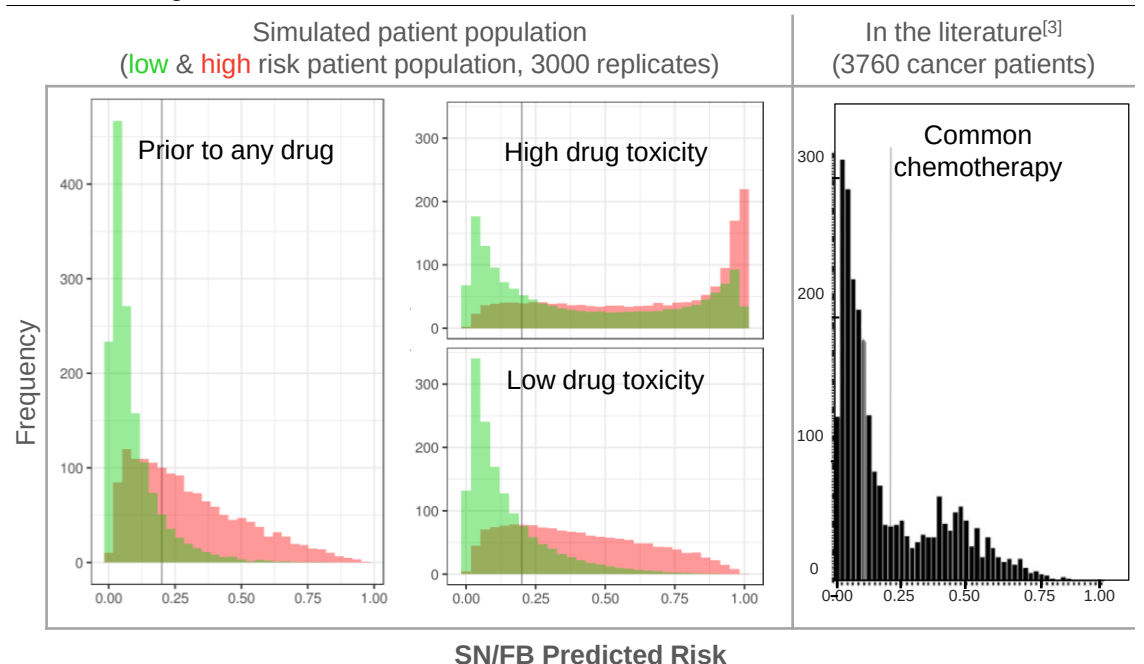
- Simulation process for each scenario
 - Sample 6 patient baseline risks from the predicted risk distribution prior to any drug (left panel on Fig.1)
 - Add the dose-related drug effect to the baseline risks
 - Simulate one event (0/1) based on the risk probability for each dose and each patient
 - Count events at each dose across the 6 patients
 - Derive MTD using its operational definition
- This process was simulated 1000 times to obtain the predictive distribution of MTD values
- Simulations and plots were performed in R (v. 3.5.1).

Results

1. Distribution of predicted risks of SN/FB

- Two sets of patient covariates were simulated
 - Low risk population:** age <65 year, breast cancer, no prior chemotherapy, normal white blood cells, normal liver cells and normal renal function
 - High risk population:** age ≥ 65 years, small-cell lung cancer, prior chemotherapy, low white blood cells, elevated liver enzymes and moderate renal impairment
- The predicted $p_{SN/FB}$ distributions prior to treatment and post Low/High drug treatment are illustrated in both populations and compared to literature (Fig.1)

Figure 1. SN/FB risk distributions in the 3000 simulations and in literature.

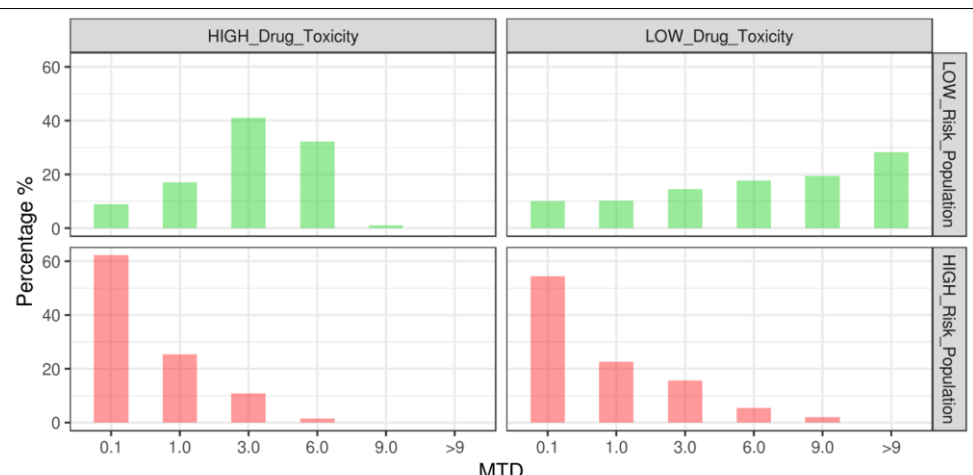


- Risk distributions from the simulation case are in line with literature
- The threshold of $p_{SN/FB} = 0.2$ recommended by guideline for prophylactic treatment [3,4] separates pretty well the two populations (— in Fig.1)

2. MTD distribution

- Clear shift in the MTD distributions between the low and high-risk populations, irrespective of the level of drug toxicity.
- For the low-toxicity drug, the most likely MTD was at the high doses (9 mg and above) in the low-risk population, and across doses (0.1 to >9 mg) in the high-risk population. For the high-toxicity drug, the most likely MTDs in low-risk population and high-risk population were up to 9 mg and up to 6 mg respectively.

Figure 2. Predictive MTD distributions from 1000 dose escalation trials (5 doses and 6 patients per dose, sampled either a low or high risk population)



Conclusions

- This simulation work illustrates the importance of accounting for risk factors in the MTD concept, determination and application for dose finding
- Expansion of the work by testing other neutropenia risk models^[4] is ongoing
- This simulation work may be applied in oncology early development to better design Phase I MTD determination process

References

- [1] Symposium. Challenging the maximum tolerated dosing paradigm in oncology: Threading the needle with targeted agents. ASCPT Annual Meeting (Atlanta, GA, March 2014).
- [2] Casabianca *et al.* Literature Review to Explore the Risk Factors of Neutrophil Toxicity in Oncology. PKUK November 2018
- [3] Lyman *et al.* Predicting Individual Risk of Neutropenic Complications in Patients Receiving Cancer Chemotherapy. Cancer. (2011); 117(9)
- [4] Aagaard *et al.* Development and validation of a risk score of febrile neutropenia after chemotherapy in patients with cancer: the FENCE score. JNCI Cancer Spectrum (2018) 2(4)

Acknowledgement

Paul Casabianca and Nuria Buil Bruna who contributed to this work plans, elaboration and review

