

A new model-based approach to compare toxicity of a series of compounds based on their categorical toxicity scores



Leiden Experts on
Advanced
Pharmacokinetics &
Pharmacodynamics

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Introduction

- The toxicity of a series of new antibody-drug conjugates (ADC's) was assessed pre-clinically and was summarized per tissue in different categories.
- Ranking the ADC's according to their toxicity facilitates pre-clinical screening.
- This requires looking at the profiles as whole by establishing concentration-response relationships for toxicity of each compound/tissue.
- The drug effect parameters of the concentration-response relationships for toxicity may not be compared directly since they are highly dependent on the baseline probabilities of the different scores.

Objectives

The objective of this analysis was to develop a method to utilize the outcome of proportional odds models for comparison of the toxicity of a series of ADC's for pre-clinical screening.

Methods

A stepwise approach was followed:

Step 1: Concentration-response relationships for toxicity of compounds/tissues were established.

Step 2: A measure was derived from the slope of the drug effect and cumulative probabilities between cutpoints to compare the toxicity of a series of ADC's.

Study design

- Compounds:** Series of ADC's (12 compounds)
- Study design:**
 - Single-endpoint studies in rats
 - Vehicle and 3 different dose levels per compound
 - N= 5-10 per dose group
 - Vehicle group for each compound/tissue differs in size
 - Toxicity investigated in up to 6 different tissues
 - Heart, lung, liver, kidney, bone marrow (BM) and eye
 - All tissues were investigated for each compound, but not all tissue showed clinical signs of toxicity for a particular compound
 - Toxicity scores based on histopathology
 - Score range 0 (not toxic) – 4 (very toxic)
 - The 5 categories the score considers do not all occur for each compound/tissue combination

Model

Step 1: Model structure: *Proportional odds model*^[1]

- Ordered categorical data (Y= 0,1,2,3 or 4)
- All probabilities can be obtained by modeling cumulative probabilities:
 $P(Y=0) = 1 - P(Y>0)$
 $P(Y=1) = P(Y>0) - P(Y>1)$
 $P(Y=2) = P(Y>1) - P(Y>2)$
 $P(Y=3) = P(Y>2) - P(Y>3)$
 $P(Y=4) = P(Y>3)$
- Parameterized so that $P(Y>1) > P(Y>2)$
 - On logits scale (log odds)
- Drug effect causes proportional change in distribution probabilities between observed grades
- ω fixed to zero, as no repeated measurements within subject were made
- Odds = $p/(1-p)$
- Exposure expressed as Cavg

Fragment NONMEM model code

```

; Cumulative logit
$PRED
C1 = THETA(1) + ETA(1)
C2 = THETA(1) + THETA(2) + ETA(1)
C3 = THETA(1) + THETA(2) + THETA(3) + ETA(1)
C4 = THETA(1) + THETA(2) + THETA(3) + THETA(4) + ETA(1)
;
SLOPE=THETA(5)
;
E1=C1 - SLOPE*Cavg
E2=C2 - SLOPE*Cavg
E3=C3 - SLOPE*Cavg
E4=C4 - SLOPE*Cavg
; Cumulative probabilities between cut points
EFF1=EXP(E1)/(1+EXP(E1))
EFF2=EXP(E2)/(1+EXP(E2))
EFF3=EXP(E3)/(1+EXP(E3))
EFF4=EXP(E4)/(1+EXP(E4))
;
P1 = EFF1
P2 = EFF2 - EFF1
P3 = EFF3 - EFF2
P4 = EFF4 - EFF3
P5 = 1 - EFF4
; Likelihood contribution, NB not densities
IF (DV.EQ.0) Y = P1 ; score 0
IF (DV.EQ.1) Y = P2 ; score 1
IF (DV.EQ.2) Y = P3 ; score 2
IF (DV.EQ.3) Y = P4 ; score 3
IF (DV.EQ.4) Y = P5 ; score 4
```

$$\logit[P(Y \geq j)] = C_j - slope * Cavg$$

$$j = 1, \dots, 4$$

Step 2: Model based method for ranking

a) "PC₅₀'s" were derived from slope and cumulative probabilities between cutpoints

- PC₅₀x is defined as the concentration where the probability of score x is reduced by half**
 - PC₅₀0 is defined as the concentration where the probability of score 0 is reduced by half:

$$0.5 \cdot \frac{e^{-C_1}}{1 + e^{-C_1}} = \frac{e^{-C_1 + slope \cdot Cavg}}{1 + e^{-C_1 + slope \cdot Cavg}} \Rightarrow PC_{50}0 = \frac{LN\left(\frac{0.5}{0.5 \cdot e^{-C_1} + 1}\right)}{-slope}$$

- PC₅₀1 is defined as the concentration where the probability of score 1 is reduced by half:

$$0.5 \cdot \left(\frac{e^{-C_2}}{1 + e^{-C_2}} - \frac{e^{-C_1}}{1 + e^{-C_1}} \right) = \frac{e^{-C_2 + slope \cdot Cavg}}{1 + e^{-C_2 + slope \cdot Cavg}} - \frac{e^{-C_1 + slope \cdot Cavg}}{1 + e^{-C_1 + slope \cdot Cavg}} \Rightarrow PC_{50}1 = \frac{LN\left(\frac{e^{-C_2} - e^{-C_1}}{e^{2C_2} - e^{2C_1} - 2e^{C_2} + 2e^{C_1} - 2e^{2C_1+C_2} + 2e^{C_1+2C_2}}\right)}{-slope}$$

- PC₅₀2 is defined as the concentration where the probability of score 2 is reduced by half:

$$PC_{50}2 = \frac{LN\left(\frac{e^{-C_3} - e^{-C_2}}{e^{2C_3} - e^{2C_2} - 2e^{C_3} + 2e^{C_2} - 2e^{2C_2+C_3} + 2e^{C_2+2C_3}}\right)}{-slope}$$

- PC₅₀3 is defined as the concentration where the probability of score 3 is reduced by half:

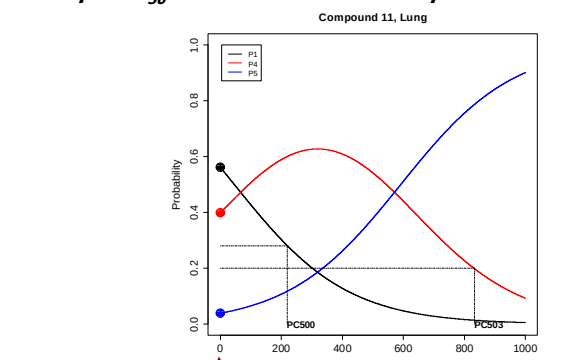
$$PC_{50}3 = \frac{LN\left(\frac{e^{-C_4} - e^{-C_3}}{e^{2C_4} - e^{2C_3} - 2e^{C_4} + 2e^{C_3} - 2e^{2C_3+C_4} + 2e^{C_3+2C_4}}\right)}{-slope}$$

b) PC₅₀'s were normalized by the ADC's tumor static concentrations (TSC):

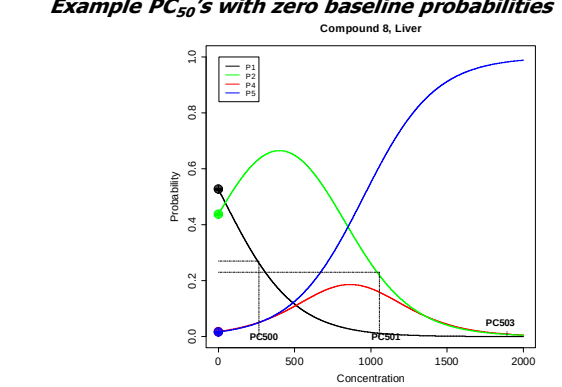
- TSC is the concentration where tumor growth and death rates are equal and tumor volume remains unchanged. By normalizing with the TSC's, the efficacy of the ADC's is taken into account.

$$tox\ score = \frac{PC_{50}x}{TSC}$$

Example PC₅₀'s with nonzero baseline probabilities



Example PC₅₀'s with zero baseline probabilities

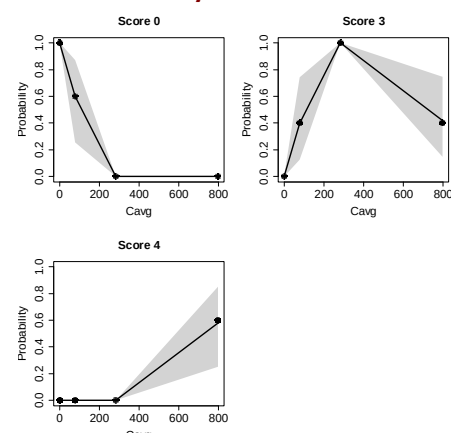


Results

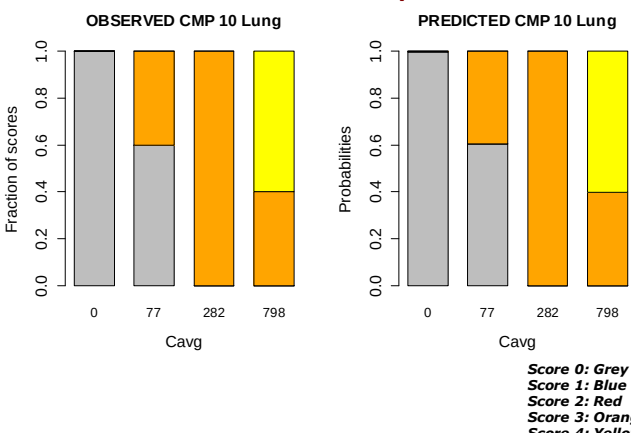
Step 1: Description concentration-response for toxicity

Example description compound 10, lung:

Visual predictive check

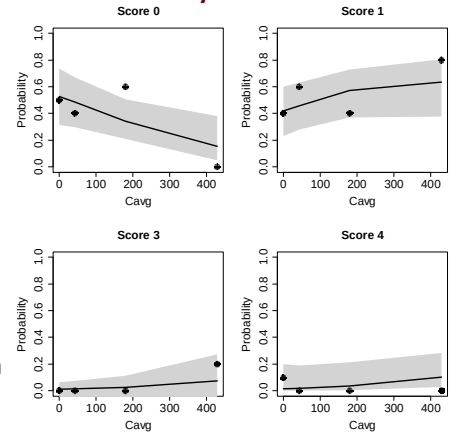


Goodness of fit plot

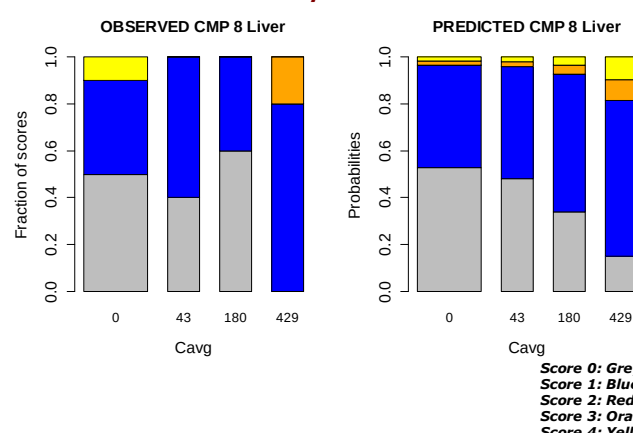


Example description compound 8, liver:

Visual predictive check



Goodness of fit plot



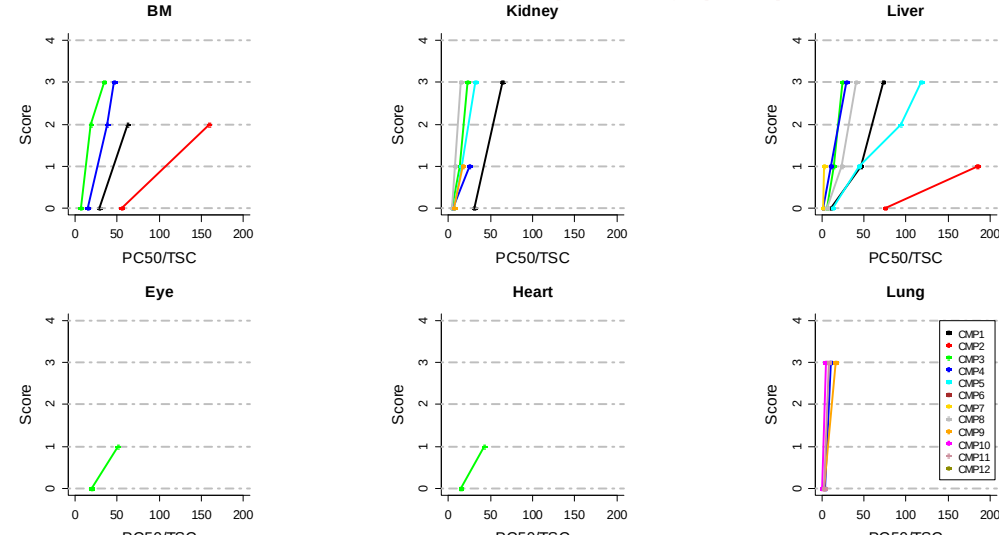
Step 2: Model based method for ranking

- The different compounds were compared using PC₅₀'s
- PC₅₀'s were determined for the series of ADC's and different tissues.
 - Not all PC₅₀'s can be calculated for each compound/tissue as not all scores occur for each compound/tissue
- PC₅₀'s were normalized by their TSC
 - TSC is an efficacy index

- The smaller the value of the derived tox score (PC₅₀x/TSC), the more toxic the compound**
 - E.g. compound 3 is more toxic in bone marrow than compounds 1, 2 and 4
- The distance between PC₅₀'s, equivalent to the steepness in the graphical representation, is also informative on the toxicity of the compound.
 - E.g. compound 5 is less toxic than compound 4 in the liver.

PC ₅₀ 's:												Normalization:			
COMPOUND	TISSUE	TISS	PC500	PC501	PC502	PC503	TSC	PC500/TSC	PC501/TSC	PC502/TSC	PC503/TSC				
1	BM	1	244.16	521.71	8.40	29.07	62.11								
2	BM	1	115.44	335.18	2.10	54.97	159.61								
3	BM	1	31.88	89.52	168.61	4.90	6.51			18.27	34.41				
4	BM	1	308.85	771.01	928.56	20.30	15.21			37.98	45.74				
6	BM	1	15.36	38.38	60.16										
1	Kidney	2	257.78		535.63	8.40	30.69				63.77				
3	Kidney	2	20.73	68.25	113.49	4.90	4.23			13.93	23.16				
4	Kidney	2	106.13	496.73		20.30	5.23			24.47					
5	Kidney	2	44.92	111.96		232.94	7.22			6.22	32.26				
8	Kidney	2	169.98	364.89		687.66	46.1			3.69	7.92				
9	Kidney	2	324.24	797.90		46.1	7.03			17.33					
1	Liver	3	94.62	392.50	612.29	8.40	11.26			46.73	72.89				
2	Liver	3	156.62	388.82		2.10	75.53			185.15					
3	Liver	3	29.72	69.70	4.90	120.89	6.06			14.23	24.67				
4	Liver	3	33.73	209.89		601.62	20.30			1.66	10.34				
5	Liver	3	91.91	320.81	673.64	850.31	7.22			12.73	44.43				
7	Liver	3	156.93	343.59			126			1.25	2.73				
8	Liver	3	265.22	1055.96		1892.98	46.1			5.75	22.91				
3	Eye	4	97.43	248.33			19.88			50.68	41.06				
3	Heart	5	70.62	208.44			4.90			14.45	42.54				
3	Lung	6	14.97			55.26	4.90			3.05	11.28				
4	Lung	6	75.25			206.31	20.30			3.71	10.16				
8	Lung	6	111.95				46.1			2.43					
9	Lung	6	128.80			748.69	46.1			2.79					
10	Lung	6	83.00			884.94	183.5			0.45					
11	Lung	6	219.85			834.02	104.2			2.11					
12	Lung	6	NA			NA	NA			NA					

Derived tox scores presented graphically:



Conclusion & Perspectives

- A new model-based method was developed to easily assess and compare categorical toxicity scores.
- PC₅₀'s were derived from the slope and the cumulative probabilities between cutpoints.
- TSC's were used to normalize the PC₅₀'s to derive a tox score.
 - These tox scores gave similar ranking results as an external validation method (not shown).
 - The values of these tox scores as well as the distance between them within a compound/tissue were found to be informative on the toxicity of the compound.
- The developed method can be used for rapid compound screening (e.g. linker-payload screening) during ADC discovery and development.
- The method offers an objective and more informative insight into the toxicity profile of ADC's by providing tox scores relative to efficacy as well as the steepness of the exposure response (distance between scores).