

Data-driven assessment of the association of polymorphisms in 5-Fluorouracil metabolism genes with outcome in adjuvant treatment of colorectal cancer

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Disclaimer

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The benefit-risk balance.....







Introduction



Patient group

HTA

New fantastic drug!



EMA

FDA





Aim

• A data-driven assessment with focus on:

- transparency
- clinical significance
- visualisation
- communication



Contents

- Background
- Material
- Method
- Results
- Conclusions



Background

Afzal and co-workers demonstrated that specific combinations of functional polymorphisms in dihydropyrimidine dehydrogenase (DPYD) and thymidylate synthase (TYMS) polymorphisms were associated with increased DFS in colorectal cancer patients recieving adjuvant 5-FU based treatment, HR 0.69 [0.49 – 0.98].*

*Afzal S, Gusella M, Jensen SA, Vainer B, Vogel U, Andersen JT, et al.

The association of polymorphisms in 5-fluorouracil metabolism genes with outcome in adjuvant treatment of colorectal cancer. Pharmacogenomics 2011 Sep;12(9):1257-67.



Material

	Number of patients (N= 302)		
MDR-1	111		
MDR-0	158		
Missing	33		

The MDR-1 group consists of patients with the combination of variant alleles in the DPYD gene and the TYMS VNTR polymorphism, selected by the Multifactor Dimentionality Reduction algorithm as being associated with improved DFS.









- The question: How well do two groups (MDR-1 and MDR-0) of patients with the same disease, but different genetics respond to the same treatment?
- Disease: Colorectal cancer.
- Treatment: Chemotherapeutic agent (5-FU).
- The aim: A head to head comparison on
 - Cure rate, survival rate, time-to-death (TTD), time-to-relapse (TTR), and main adverse events.
- Expectations: Based on former knowledge, we expect that the specific combination of genetic polymorphisms in the MDR-1 group will have an advantage with reference to DFS.





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2: Decision profile

Criterion	Weight	Score	Weighted Score
Survival rate			
Cure rate			
TTD			
TTR			
Infection			
Myocardial ischemia			
Bleeding			
Mucositis/Stomatitis			
Hand-foot skin syndrome			
Diarrhea			
Arthralgia/Myalgia			
Fatigue			
Nausea/Vomiting			





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3: Weighting

Criterion	Weight	Score	Weighted Score
Survival rate	3		
Cure rate	3		
TTD	3		
TTR	3		
Infection	2		
Myocardial ischemia	2		
Bleeding	2		
Mucositis/Stomatitis	2		
Hand-foot skin syndrome	2		
Diarrhea	2		
Arthralgia/Myalgia	1		
Fatigue	1		
Nausea/Vomiting	1		









4: Scoring

Relative scoring

For each criterion, MDR-1 is scored relative to MDR-0

Criterion	Score
MDR-1 is superior	+1
MDR-1 is non-inferior	0
MDR-1 is inferior	-1





4.1: Difference Distribution Scoring

Clinical relevance:

- a difference is considered relevant if a substantial part of the subjects experience better performance with either drug or comparator.
- the extent of the substantial part depends on disease area and decision context.
- In the current setting 12 out of 20 (=60%) patients experiencing an effect, is defined as clinically relevant.





4.1: Difference Distribution Scoring



18



4.1: Confidence Interval Scoring

- For events the question is:
 - is the probability, p, of one event/subject different between MDR-1 and MDR-0?





4.1: Confidence Interval Scoring







4.1: Confidence Interval Scoring



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4.1: Confidence Interval Scoring



95 % confidence level



20 Events for MDR-1 / stomatitis 5 Mvo ${\rm O}$ \bigcirc Bleeding **Fatigue** 00 10 15 20 25 30 Events for MDR-0 (N = 158)

66,7 % confidence level







5: Evaluation of uncertainty

- In case of any uncertainty the score may be given as an interval $(-1 \rightarrow 0, 0 \rightarrow 1 \text{ or } -1 \rightarrow 1)$.
 - 1. Qualitative evaluation*:
 - Evaluate methodological flaws/deficiencies and their impact.
 - Describe any negative studies, studies showing no difference.
 - 2. Quantitative evaluation:
 - Quantitative evaluations can be performed by the use of resampling.



5: Evaluation of uncertainty

- Interval-scores are assigned to following borderline criteria:
 - Infections
 - Arthralgia/Myalgia
 - Fatigue





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Criterion	Weight	Score	Weighted Score
Survival rate			
Cure rate			
TTD			
TTR			
Infection			
Myocardial ischemia			
Bleeding			
Mucositis/Stomatitis			
Hand-foot skin syndrome			
Diarrhea			
Arthralgia/Myalgia			
Fatigue			
Nausea/Vomiting			

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Criterion	Weight	Score	Weighted Score
Survival rate	3		
Cure rate	3		
TTD	3		
TTR	3		
Infection	2		
Myocardial ischemia	2		
Bleeding	2		
Mucositis/Stomatitis	2		
Hand-foot skin syndrome	2		
Diarrhea	2		
Arthralgia/Myalgia	1		
Fatigue	1		
Nausea/Vomiting	1		

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Criterion	Weight	Score	Weighted Score
Survival rate	3	1	
Cure rate	3	1	
TTD	3	1	
TTR	3	0	
Infection	2	-1	
Myocardial ischemia	2	-1	
Bleeding	2	0	
Mucositis/Stomatitis	2	1	
Hand-foot skin syndrome	2	0	
Diarrhea	2	0	
Arthralgia/Myalgia	1	0	
Fatigue	1	1	
Nausea/Vomiting	1	0	

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Criterion	Weight	Score	Weighted Score	
Survival rate	3	1		
Cure rate	3	1		
TTD	3	1		
TTR	3	0		
Infection	2	- 1 → 0		
Myocardial ischemia	2	-1		
Bleeding	2	0		
Mucositis/Stomatitis	2	1		
Hand-foot skin syndrome	2	0		
Diarrhea	2	0		
Arthralgia/Myalgia	1	0→-1		
Fatigue	1	$1 \rightarrow 0$		
Nausea/Vomiting	1	0		

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Criterion	Weight	Score	Weighted Score		
Survival rate	3	1	3		
Cure rate	3	1	3		
TTD	3	1	3		
TTR	3	0	0		
Infection	2	- 1 → 0	-2→ 0		
Myocardial ischemia	2	-1	-2		
Bleeding	2	0	0		
Mucositis/Stomatitis	2	1	2		
Hand-foot skin syndrome	2	0	0		
Diarrhea	2	0	0		
Arthralgia/Myalgia	1	0 → -1	0 → - 1		
Fatigue	1	$1 \rightarrow 0$	$1 \rightarrow 0$		
Nausea/Vomiting	1	0	0		









7: Presentation

	MDR-1 inferior	1 MDR-1 r non-inferior		MDR-1 superior	
Survival rate					
Cure rate					
ТТD					
TTR					
Infection					
Myocardial ischemia					
Bleeding					
Mucositis/stomatitis					
Hand-foot skin reaction					
Diarrhoea					
Arthralgia/myalgia					
Fatigue					
Nausea/vomiting					









8: Overall conclusion

The assessment is concluded by:

- A clinically significant and relevant difference for the high importance criteria cure rate, survival rate, and TTD was found in favour of the MDR-1 group.
- A higher risk of severe cases of the medium importance criterion myocardial ischemia and a slightly higher risk for the medium importance criterion infection were seen in the MDR-1 group.
- The clinical implications of this study are that genetic profiling is advisable in patients with colorectal cancer, to enable individualised treatment and follow-up.



Conclusions

- We have demonstrated a comprehensive approach to datadriven benefit-risk assessments and how it can be used in a clinical setting.
- The method can handle a variety of different types of clinical data and can be used in a single study as well as on multiple studies.



Conclusions

- Transparency in decision making increase credability of the assessment and can be secured by:
 - Following a structured framework
 - Justification of choices at critical steps in the assessment
 - Being consistent with previuos decisions



Conclusions

- Discussion of clinical significance of data support decision making in greater perspective and can be incorporated by:
 - Considering proportion of patients experiencing an effect
 - Being proactive and looking for tendencies in sparse data, instead of rejecting any signal due to high confidence level
- Visualisation tools help comprehend more data at the same time.



Take home message



Experies et es a tree évolutes some et anch gories atte inpution trade lly...



Thank for your attention!

