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The clinical utility of a change in the Royal Marsden Hospital Prognostic Score (RMHPS) in patients prior to phase I clinical trial therapy

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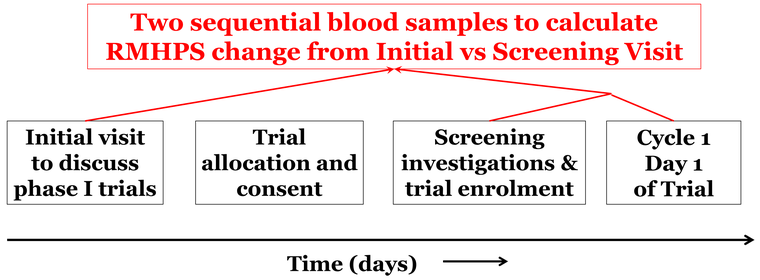
C.O Michie, **M. Ong**, J. Mateo, A.M. Young, D. Olmos, J.E.Ang, L.R. Molife, U. Banerji, J.S. De Bono, S.B. Kaye

ICR/RMH Drug Development Unit, Royal Marsden Hospital, Sutton, London, United Kingdom

Background / Methods

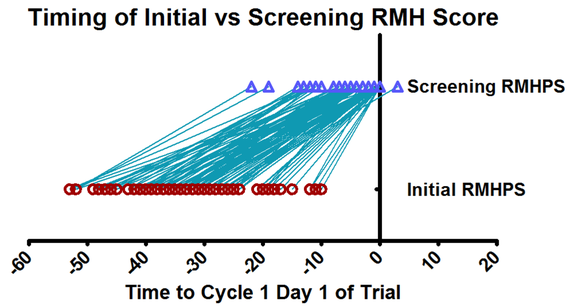
- Patient selection for phase I oncology trials presents an ongoing challenge.
- Usually life expectancy >3 months is a key trial eligibility criterion; however, accurate assessment of life expectancy is difficult in patients with advanced, treatment-refractory cancer[1].
- One in 7 phase I trial patients withdraws within 21 days of starting a phase I trial[2], rendering them non-evaluable for study purposes and requiring replacement within the trial.
- ECOG performance status (PS) is powerful prognostic factor[2-3] but is limited inherent subjectivity.
- We previously developed and validated the Royal Marsden Hospital prognostic score (RMHPS) to help guide appropriate patient selection[4]. The RMHPS is calculated by one point each for: **serum albumin (Alb) <35, lactate dehydrogenase (LDH) >ULN, and number metastatic sites >2**.
- 0-1 is a low score (favourable prognosis); 2-3 is a high score (unfavourable).
- Despite its prognostic utility, strict adherence to the RMHPS would require an overall reduction in trial recruitment of 20% in order to reduce non-drug-related 90-day mortality[2], potentially excluding suitable patients.
- In this study, we assessed whether accounting for change in the RMHPS during the trial screening process may improve the predictive discriminatory ability of this tool to identify patients most likely to withdraw early (< 30days) from a phase I clinical trial for reasons other than trial drug toxicity.



- **Patient Population:** 131 patients treated in a phase I clinical trial who entered a parallel biomarker study between Sep 2009 – Sep 2011 at the RMH Drug Development Unit were identified from a prospectively collected database. Data including ECOG PS, LDH, Albumin, phase I trial drug, trial start and stop dates, reason for trial discontinuation, last follow-up date and survival were collected. Laboratory data were collected independently and blinded to clinical outcome.
- **RMHPS Analysis:** RMHPS was calculated at both initial visit and during the screening process prior to starting trial treatment. RMH prognostic scores of 0-1 and 2-3 were denoted low and high, respectively. Patients were separated into four groups, based on the two sequential RMH scores: low-low, low-high, high-low, and high-high score. Median survival times and time to study withdrawal were estimated by the Kaplan-Meier method, and prognostic variables were compared in multivariate Cox regression analysis.

References 1 Arkenau, Brit J Cancer 2008; 2 Olmos, J Clin Oncol 2012; 3 Ploquin, Crit Rev Oncol Haematol 2012; 4 Arkenau, J Clin Oncol 2009.

Results



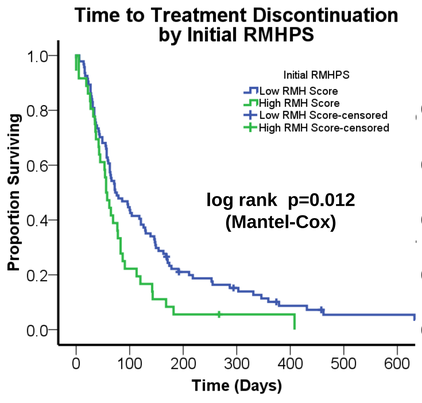
Timing of RMHPS Calculations;

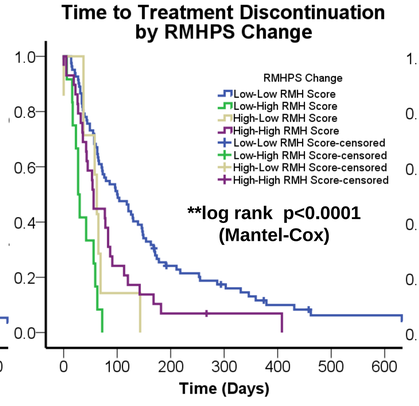
	Initial RMHPS	*Screening RMHPS*
Mean Time (days) before C1D1 [range]	-32 [-53 to -10]	-4 [-22 to 3]
Standard Deviation	*9.3*	*4.5*
Mean Time from Initial Visit to Screening	28 [10 to 52]; *SD 7.2*	

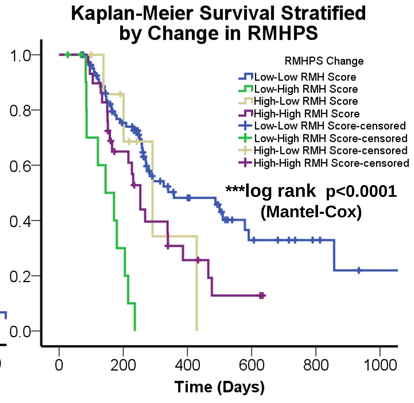
Patient Characteristics and Outcome; Stratified by RMHPS Change;

Change in RMHPS	*Low to Low 82 (62.6%)*	*Low to High 12 (9.2%)*	*High to Low 8 (6.1%)*	*High to High 29 (22.1%)*	*All patients (n=131)*
Colorectal	7 (25%)	4 (14%)	2 (7%)	15 (54%)	*28 (21%)*
Ovary	15 (63%)	3 (13%)	0 (0%)	6 (25%)	*24 (18%)*
Breast	15 (75%)	0 (0%)	3 (15%)	2 (10%)	*20 (15%)*
Lung	7 (78%)	2 (22%)	0 (0%)	0 (0%)	*9 (7%)*
Melanoma	6 (67%)	1 (11%)	0 (0%)	2 (22%)	*9 (7%)*
Other	32 (78%)	2 (5%)	3 (7%)	4 (10%)	*41 (31%)*
Median Age (years)	55	55	63	61	*57*
ECOG PS 0-1 at C1D1	100%	100%	100%	100%	*100%*
Female sex	59%	25%	50%	55%	*57%*
Median # prior therapy	2 (1-7)	2 (1-4)	2.5 (1-5)	3 (1-8)	*2 (1-8)*
Median # distant mets	2	2	2	3	*2*
% stop trial ≤30 days*	11%	58%	14%	21%	*18%*
Median time on phase I trial (days, 95% CI)**	100 (60-139)	27 (19-34)	62 (52-72)	56 (51-61)	*69 (57-81)*
Median survival from initial visit (days, 95% CI)***	358 (150-566)	145 (68-222)	291 (213-292)	253 (157-425)	*277 (219-335)*

*Pearson Chi-Squared p<0.001







Trial Withdrawal Reason

Progressive Disease (75%)
57 (70%) Low-Low
9 (75%) Low-High
8 (100%) High-Low
24 (83%) High-High

Drug Toxicity (9%)
7 (8.5%) Low-Low
1 (8.3%) Low-High
0 (0%) High-Low
3 (10.3%) High-High

Other Reason (16%)
21 (16%) Overall

High RMHPS at Initial Visit:
Sensitivity = 30%; Specificity = 74% for 30 day withdrawal
Sensitivity = 35%; Specificity = 77% for 60 day withdrawal

Low to High RMHPS (Deterioration in Score):
Sensitivity =44%; Specificity = 95% for 30 day withdrawal
Sensitivity = 28%; Specificity = 97% for 60 day withdrawal
LR positive = sens/(1-spec)= 6.5 (30 d) and 8.1 (60 d);
LR negative = (1-sens)/spec = =0.60 (30d) and 0.75 (60d)

A multivariate Cox regression model incorporating age, ECOG PS, and Low-High RMHPS was associated with significantly worse survival (HR 6.53, 95% CI 3.09-13.79) *(data not shown)*

Conclusions

Deterioration in RMH score from low (0-1) to high (2-3) immediately prior to phase I trial enrolment was predictive of early withdrawal and death in this data set. Patients with a low-high score change had a median time on trial of less than 30 days, with 58% of patients discontinuing trial within the dose-limiting toxicity assessment period.

This very simple, cost-effective, dual time point assessment may increase the predictive value and clinical utility of the established single measurement RMH prognostic model, identifying a specific population who withdraw early. Use of this score may help mitigate against premature withdrawal, delayed and/or more costly drug development, and exposure of poor prognosis patients to unnecessary toxicity and harm.

This data is undergoing further validation in larger data sets before recommending its routine use.

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Contact Caroline.Michie@icr.ac.uk