Development and blind clinical validation of a microRNA based predictor of response to treatment with R-CHO(E)P in DLBCL

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1. Abstract

MicroRNAs (miRNA) are a group of short noncoding RNAs that regulate gene expression at the posttranscriptional level. It has been shown that microRNAs are independent predictors of outcome in patients with diffuse large B-cell lymphoma (DLBCL) treated with the drug combination R-CHOP. Based on the measured growth inhibition of 60 human cancer cell lines (NCI60) in the presence of doxorubicine, cyclophosphamide, vincristine and etoposide as well as the baseline microRNA expression of the 60 cell lines, a microRNA based response predictor to CHOP was developed. The response predictor consisting of 20 microRNAs was blindly validated in a cohort of 116 de novo DLBCL patients treated with R-CHOP or R-CHOEP as first line treatment.

2. Patient demographics

Variable	Values	N
Sex	Male	54
	Female	62
Age	Minimum	22
	Median	63
	Maximum	86
IPI	0	10
	1	28
	2	37
	3	18
	4	16
	5	7
Treatment	R-CHOP	95
	R-CHOEP	21
Survival	Dead	22
	Alive	94
Median observation	Days	1274
Treatment response	CR	57
	CRu	42
	PR	5
	PD	2
	Dead	5
	Unevaluable	5
Relapse	Relapse	13
	No relapse*	98

* excludes patients dead before response evaluation

3. RESULTS OF PRIMARY TREATMENT

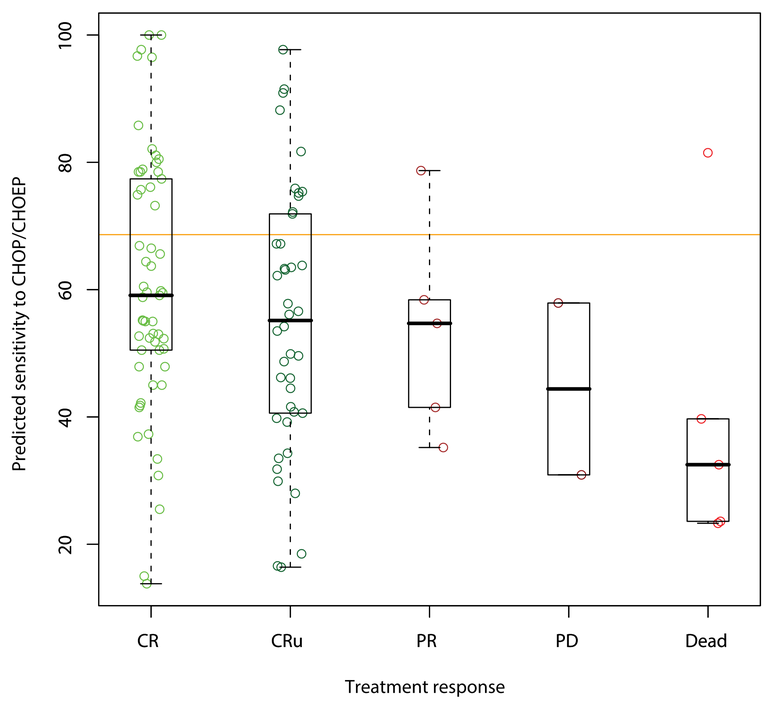

Figure 1. Correlation between predicted sensitivity to CHOP/CHOEP and response to treatment (CC=0.24, P=0.006). CR= Complete Remission, CRu= Complete Remission unconfirmed, PR=Partial Remission, PD=Progressive Disease, Dead=dead before response evaluation. A Wilcoxon rank test comparing CR to all other responses gives a p-value of 0.03. The pre-specified cutoff is shown with an orange line. The patient in the last column with a high predicted sensitivity (prediction score 82) died from a relapse within 148 days of diagnosis.

4. RESULTS OF RELAPSE TRATMENT

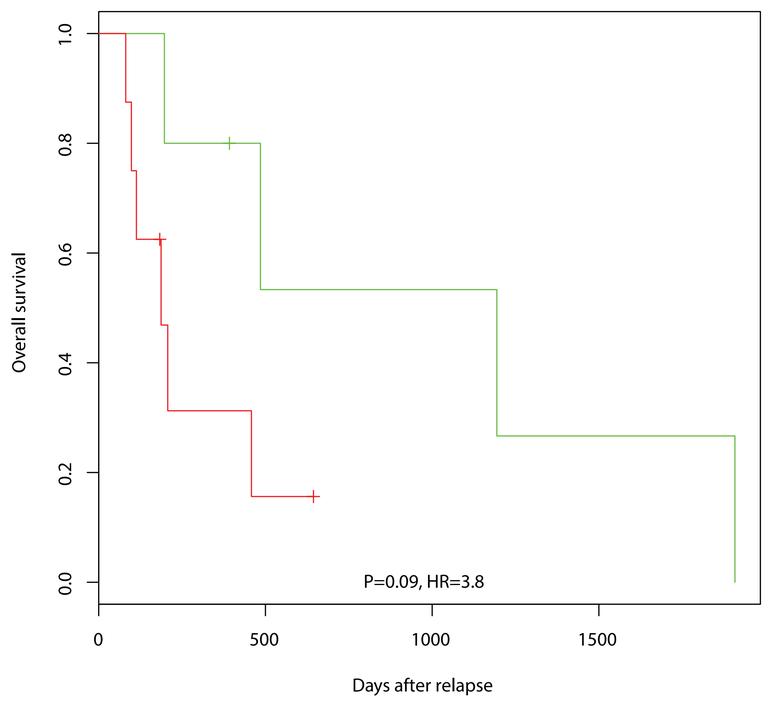

Figure 2. Overall survival after second and third line therapy among thirteen patients with disease relapse. The green line shows the Kaplan-Meier curve of five patients that are predicted sensitive to second and third line treatment received (median survival 1194 days) and the red line shows the eight patients predicted resistant (median survival 187 days).

6. CONCLUSION

In conclusion, we have developed predictive miRNA profiles for DLBCL patients that can identify patients that will respond poorly to treatment with CHOP. The potential clinical utility lies in second and third line treatment, however, where the probability of response is smaller, and the number of available treatment options is large. Our results show that there is a potential that the predictor can assist in the selection of the optimal treatment among a wide variety of choices (more than 28 treatment combinations).

7. References

Knudsen S, Hother T, Grønbæk K, Jensen T, Hansen A, Mazin W, Dahlgaard J, Møller MB, Ralfkiær E, de Nully Brown P (2015) Development and blind clinical validation of a microRNA based predictor of response to treatment with R-CHO(E)P in DLBCL. PLoS One, In press.

5. COMPARISON OF DIAGNOSTIC AND RELAPSE BIOPSIES

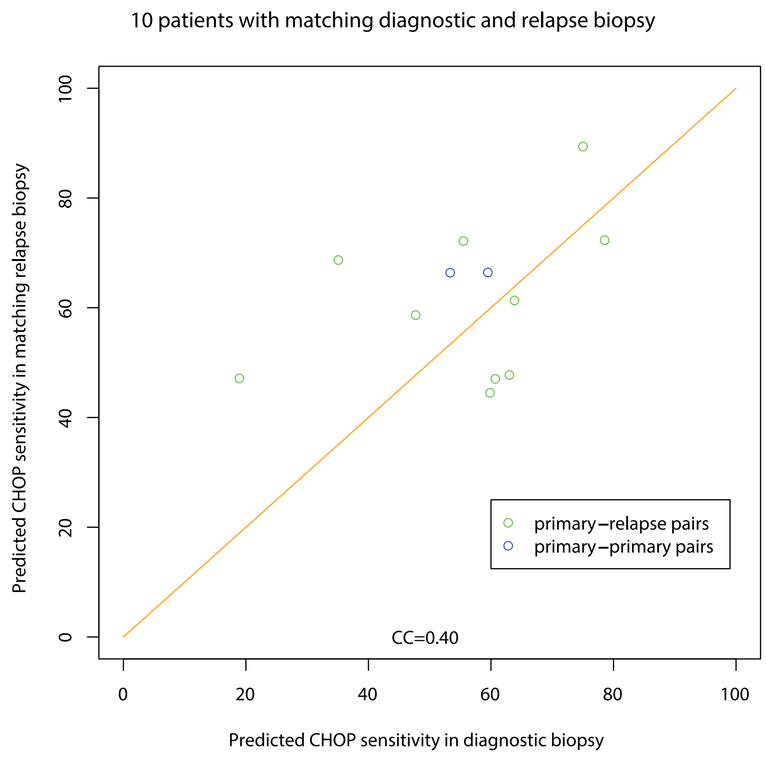

Figure 3. Comparing diagnostic and relapse biopsies. Matching primary-relapse biopsy pairs from the same patient (green) and primary-primary biopsy pairs from the same patient (blue). The orange diagonal indicates where the prediction for each biopsy in a pair is identical.