DNA Damage Response Deficiency Assay predicts response to treatment in ovarian cancer

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Introduction

- Ovarian cancer is the leading cause of death from gynaecological malignancies
- The standard first line therapy is a combination of carboplatin and paclitaxel
- The response rate is 70%-80%, although the majority relapse
- We have previously developed a 44 transcript DNA damage response deficiency (DDRD) assay which indicates loss of the FA/BRCA pathway and predicts response to DNA damaging agents
- In this study we have investigated the utility of the DDRD assay predicting response to platinum based therapy in ovarian cancer

The FA/BRCA Pathway

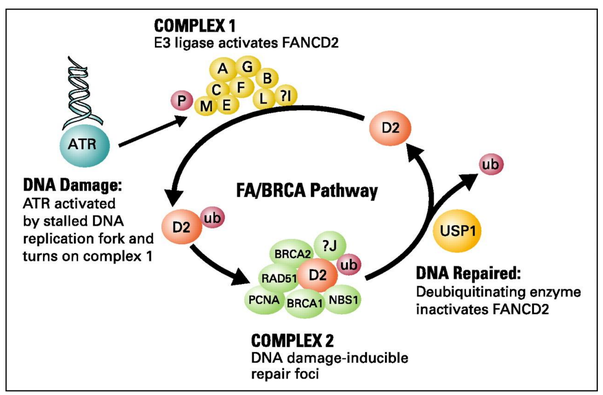

Figure 1 Loss of the FA/BRCA pathway estimated to occur in over 50% of HGS ovarian cancer

Kennedy and D'Andrea JCO 2006:24(23):3799-808

Methods

- The assay was applied to a combined set of 912 high grade serous ovarian cancer samples from 4 independent cohorts [PMID: 22348014; PMID: 18698038; doi:10.1038/nature10166; ASCO 2011 abstract #5000] receiving adjuvant platinum based chemotherapy following surgical debulking
- Data was pre-processed using RMA and DDRD signature scores generated for each sample

Table 1: Clinical characteristics of patients

Clinical characteristic	Clinical factor value	N	% samples
FIGO stage	1	20	2%
	2	49	5%
	3	690	76%
	4	142	16%
	Unknown	11	1%
Debulking	Optimal (<1cm)	471	52%
	Suboptimal(≥1cm)	335	37%
	Unknown	106	11%
Response	Complete response	390	43%
	Partial response	152	17%
	Stable disease	44	5%
	Progressive disease	59	6%
	Unknown	267	29%
Treatment	Platinum only	215	24%
	Platinum + Taxane	697	76%
Recurrence/ Non-recurrence	Recurrence	720	79%
	Censored recurrence	192	21%
Died/Alive	Died	601	66%
	Alive	311	34%

- The 70th percentile of the signature score distribution was used to classify patients, where 30% of samples were classified as DDRD-positive and 70% as DDRD-negative
- The statistical significance of the difference in survival distributions was tested using the log-rank test
- Cox proportional hazards regression was used to investigate the prognostic effect of the DDRD signature on recurrence free and overall survival , adjusting for debulking and FIGO stage

DDRD Assay Predicts Outcome in HGS Ovarian Cancer

- Considering patients that received platinum only treatment DDRD+ve patients had an odds ratio (OR) of 3.46 (95% CI: 2.10,4.76) for response to treatment (Figure 2)

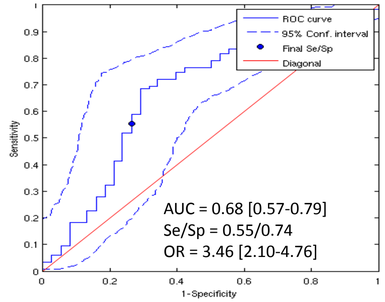

Figure 2 ROC curve for predicting response in platinum only treated high grade serous

- Overall, patients who were DDRD+ve had improved relapse free survival with a hazard ratio (HR) of 0.74 (95% CI:0.62, 0.87) on univariate analysis (Figure 3A) and 0.78 (95% CI:0.66, 0.94) on multivariate analysis (Figure 3B)
- In addition, patients who were DDRD+ve had improved overall survival with a hazard ratio (HR) of 0.61 (95% CI:0.50, 0.74) on univariate analysis (Figure 4A) and 0.75 (95% CI:0.62, 0.91) on multivariate analysis (Figure 4B)

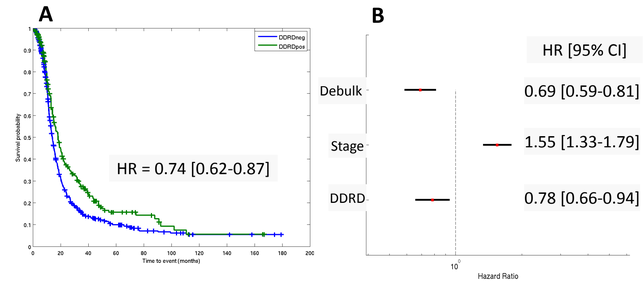

Figure 3

A) Kaplan Meier for DDRD predicting recurrence free survival
B) Forest plot of the hazard ratio from multivariate analysis

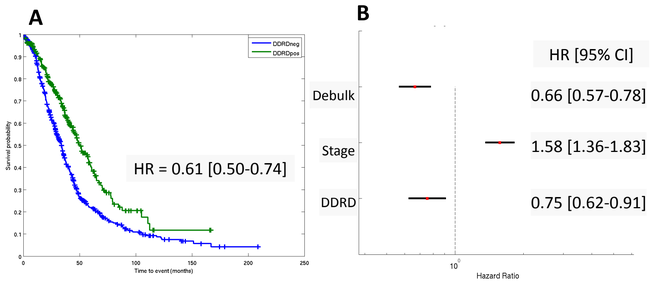

Figure 4

A) Kaplan Meier for DDRD predicting overall survival
B) Forest plot of the hazard ratio from multivariate analysis

Conclusion

- The DDRD assay predicts increased tumor response, improved progression free and overall survival following platinum-based chemotherapy in HGS ovarian cancer
- The assay is independent from other clinical factors.
- We propose that the DDRD assay could be used as a patient stratification tool for existing chemotherapy or as a clinical trial enrichment tool for DNA-damaging or repair targeted drugs in development for use in ovarian cancer