Platinum Resistance - What does it mean?

Poster Discussion 972P

Carboplatin and Gemcitabine in ‘platinum sensitive’ and ‘platinum resistant’ Ovarian cancer:
George et al

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Disclosure slide

- No financial disclosures
- Honorary Advisory Board membership
  - Roche, Boehringer Ingelheim, MSD, Clovis,
- Travel Grants
  - Boehringer Ingelheim

Recurrent ovarian cancer: population characteristics

Platinum-Free Interval (Interval from last date of platinum dose until progression)	Expected platinum sensitivity
Progression while receiving last line of platinum-based therapy or within 1 month of last platinum dose	**Refractory**
1–6 months	**Resistant**
6–12 months	**Partially sensitive**
>12 months	**Fully sensitive**

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

4th Ovarian Cancer Consensus Conference, 25–27 June 2010, UBC Life Sciences Institute, Vancouver, BC, Canada

Evidence - Rechallenge with platinum based therapy

Platinum-free Interval (months)	Response
5-12	27 %
13-24	33 %
> 24	59 %

Markman et al 1991

Time to re-challenge	Response Rate
< 1 year	17 %
1-2 years	27%
> 2 years	57%

Gore et al 1990

Definitions

- Primary Resistant
  - Progressing on primary treatment
- Secondary resistant
  - progressing on re-challenge
- Potentially sensitive
  - Sub-classified
    - < 6 months TFI
    - 6-12 months TFI
    - > 12 months TFI

Markman J Clin Oncol 1992

Response to Platinum after an interval of less than 6 months

Treatment Free interval	Cisplatin/ Paclitaxel (*de Jong et al 2002*)	Cisplatin/Etoposide (*van der Burg et al 2002*)
< 4 months	5/8	13/28 (46 %)
4-12 months	4/7	29/32 (91 %)

Do we really mean platinum-resistant disease when patients relapse within 6 months of primary chemotherapy?

Efficacy of Platinum plus Gemcitabine (G) in Platinum-Resistant (R) Compared to Platinum-Sensitive (S) Ovarian Cancer: The Royal Marsden Experience

A George, N Tunariu, S Gupta, N Wilkinson, ME Gore, SB Kaye, S Banerjee

Summary

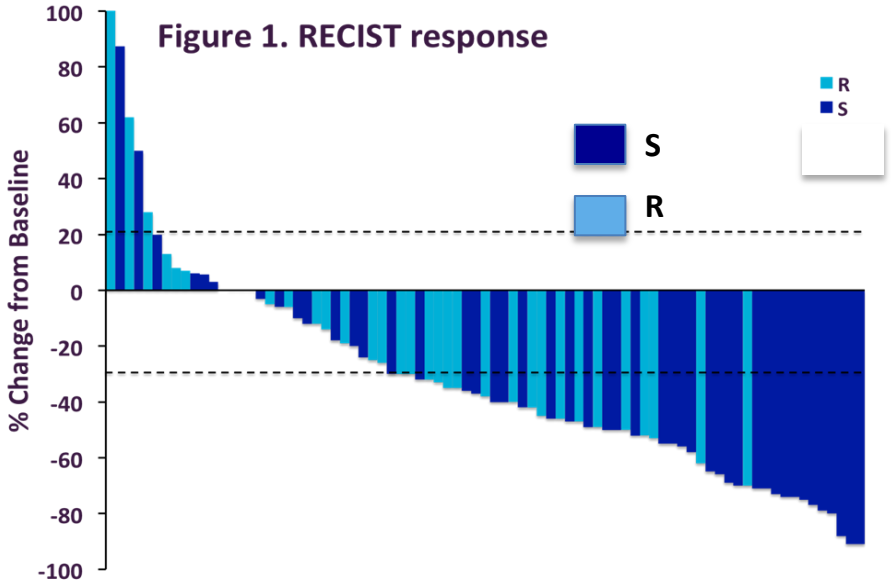
- Platinum-resistant ovarian cancer patients (< 6months platinum free interval) = **35 patients**
- Platinum-sensitive ovarian cancer= **48 patients**
- Retrospective analysis
- Carboplatin AUC 4 D1,
- Gemcitabine 800-1000 mg/m2 D1, D8 q3wk

- Primary endpoint was response rate (RR).
- Secondary endpoints included GCIG CA125 response and time to progression

- The time between last platinum and first dose of GC (LPGCI) was assessed as a predictor of response to treatment

Results

- RECIST response rates
  - **R - 57%, S – 69%**, p = 0.46
- GCIG response
  - **R – 78%, S – 82%**, p = 0.44
- PFI and LPGCI were significantly different between S and R patients
- PFI and LPGCI did not predict response (OR 1.05, 95% CI 0.99-1.11; OR 1.01, 95%CI 0.98-1.05 respectively) in S or R patients



	R	S	P value
Mean PFI (months)			
- Overall	3.71	18.25	0.0002
- Responders	3.65	20.88	0.0043
- Non-responders	3.78	12.25	<0.0001
Mean LPGCI (months)			
- Overall	13.66	22.14	0.04
- Responders	14.04	23.30	0.15
- Non-responders	13.16	19.53	0.11

Conclusions

- There was no significant difference in response for R and S patients
- Response rate appeared to be independent of both PFI and LPGCI
- The level of activity of GC in R patients is equivalent to that expected in S patients
- This may relate to the potential for G to overcome platinum resistance
- GC should now be considered a valid option for patients with platinum-resistant ovarian cancer

Platinum resistance may be partial and reversible

Phase II study of carboplatin and gemcitabine in platinum-resistant ovarian cancer

40 Patients progressing within 6 months of previous platinum-based therapy

29 % RECIST Response rate

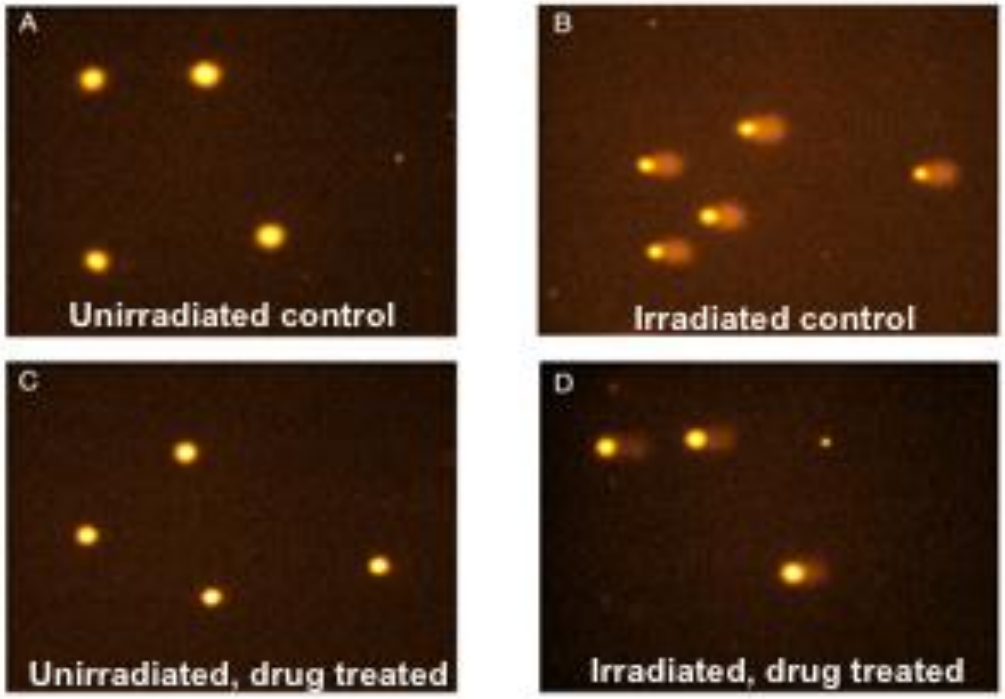
63 % CA125 GCIG response rate

Does Gemcitabine act synergistically and help to overcome platinum resistance?

Ledermann et al; Clin Cancer Res 2010; 16:4899-4905

Comet Assay

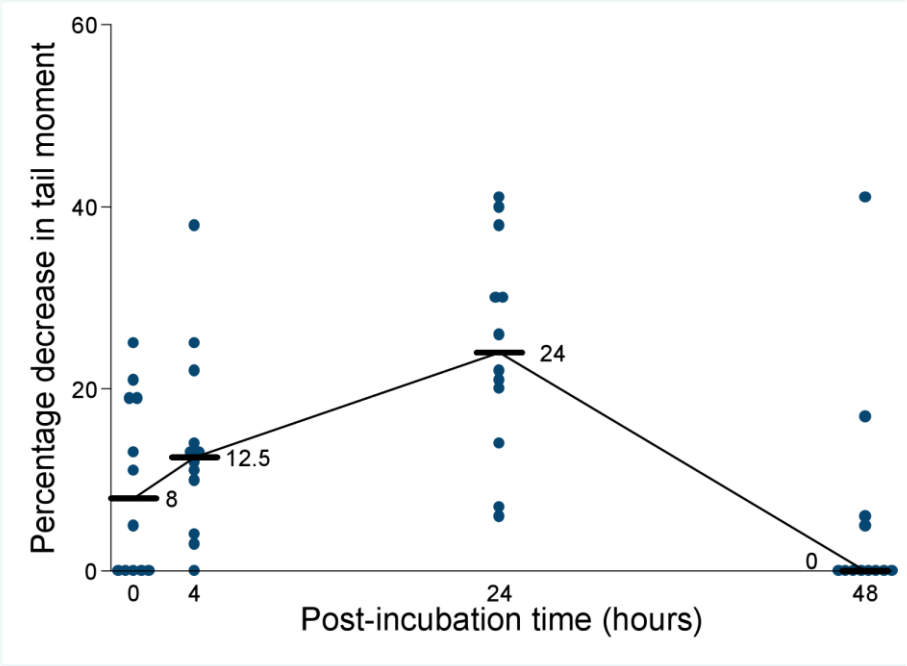
Measurement of interstand DNA Cross-links



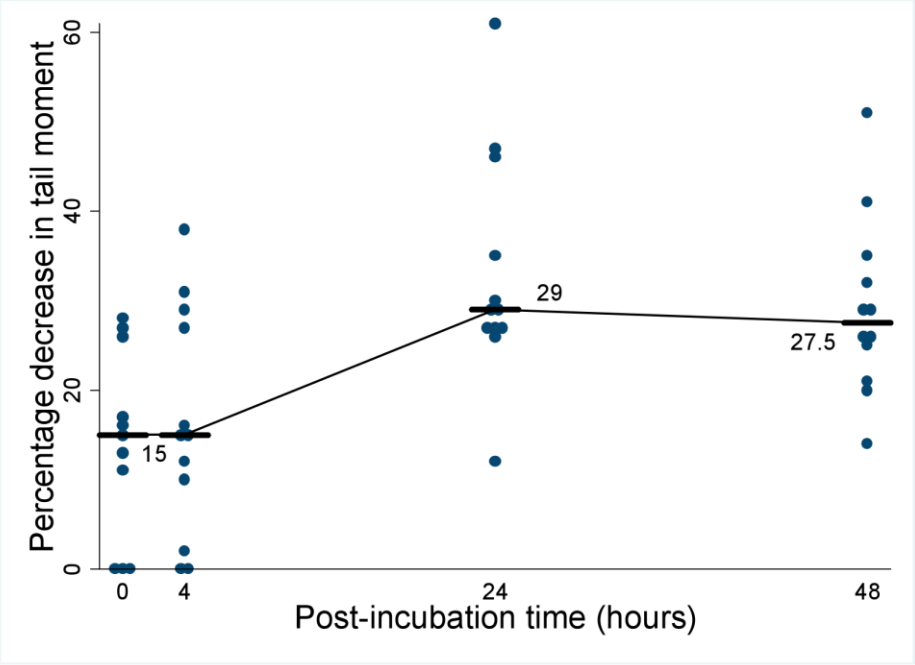
A reduction in comet tail moment is due to the presence of ICLs compared to irradiated controls. The greater the % decrease in tail moment, the greater the level of crosslinking.

Comet Assay

Formation and repair of DNA inter-strand Cross-links in PBLs of ovarian cancer patients



Carboplatin

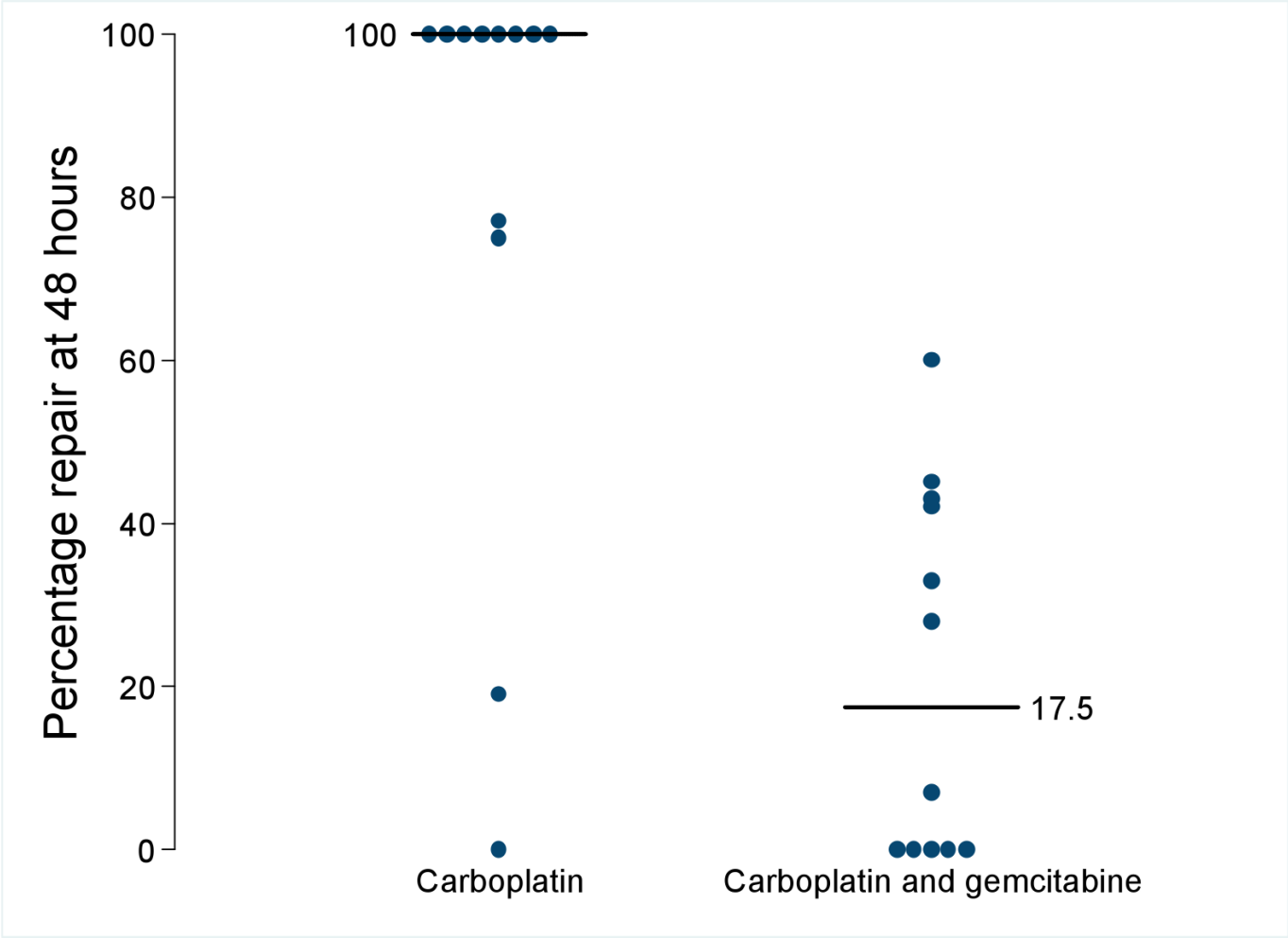


Carboplatin followed by gemcitabine

Ledermann et al; Clin Cancer Res 2010; 16:4899-4905

Repair of DNA ICLs

carboplatin with or without gemcitabine



Scheduling of Carboplatin and Gemcitabine

- No logic in giving gemcitabine without carboplatin
- Cisplatin-gemcitabine regimens' fractionate' cisplatin into Day 1 and Day regimen

Response rate in 'platinum-resistant' disease

	Regimen	Response Rate
Rose et al 2002	Cisplatin 30 mg/m^2 Gemcitabine 750 mg/m^2 D1; D 8 q 21 days	42 % [35 patients]
Nagourney et al 2002	Cisplatin 30 mg/m^2 Gemcitabine 600-750 mg/m^2 D1; D 8 q 21 days	57 % [14 patients]

Time to redefine platinum resistance

- Consider re-challenge with platinum in patients relapsing within 6 months of previous platinum treatment
- Responses are at least as good as non-platinum therapies
- Active regimens include:
  - Dose-dense platinum-based therapy
  - Platinum-gemcitabine combinations
- Future research needs to identify factors likely to predict response