Hypersensitivity to platinum salts according to BRCA status in ovarian cancer: A retrospective analysis of clinical outcomes and systematic review of literature

Original article

Title:

Hypersensitivity to platinum salts according to BRCA status in ovarian cancer: A retrospective analysis of clinical outcomes and systematic review of literature.

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Abstract:

Background: Hypersensitivity reactions (HSRs) to platinum are an important issue in the treatment of patients (pts) with ovarian cancer (OC). Germline BRCA mutations have been proposed as a risk factor. We aimed at evaluating the incidence and severity of HSRs to platinum in OC pts with known BRCA status.
Patients and Methods: We retrospectively analyzed 432 pts from 5 Italian Centers. In addition, we performed a systematic review and meta-analysis of published series.
Results: Four hundred nine pts received at least one prior platinum-based treatment line: 314 were BRCA wild type (77%) and 95 were BRCA mutated (23%). There was no statistical difference in exposure to platinum. Incidence of any grade HSRs was higher among BRCA mutated pts [9% vs 18%, p= 0.019] and the time-to-HSRs curves show that the risk increases with the duration of platinum exposure, in BRCA mutated pts more than in BRCA wild type. A multivariable analysis suggested both an increased risk in BRCA mut pts and a protective role of pegylated lyposomal doxorubicin (PLD).
The systematic review confirmed the higher incidence of HSRs in BRCA mutated pts, though heterogeneity among series was significant.
Conclusions: In OC pts with BRCA mutations, there is a significantly higher incidence of HSRs to carboplatin, not justified by longer drug exposure. On the other hand, PLD exerted a protective role in our series.

Keywords: ovarian cancer, BRCA, hypersensitivity reactions, platinum salts

Highlights:

- Hypersensitivity reactions (HSRs) to carboplatin are frequent in pretreated ovarian cancer (OC) patients (pts).
- The role of BRCA mutations (mut) as a risk factor has been suggested
- We demonstrate that BRCAmut pts have an increased risk of HSRs that is not justified by longer drug exposure only
- Receiving pegylated lyposomal doxorubicin was a protective factor in our series.
- The meta-analysis of literature, though results are heterogeneous, confirms the role of BRCAmut in increasing HSRs risk.

Introduction

Ovarian cancer (OC) is the deadliest gynecologic cancer with around 295,414 estimated new cases worldwide and about 184,799 deaths per year[1]. The majority of these women are diagnosed at an advanced stage, and a combination of radical surgery and platinum based therapy is the cornerstone of first line treatment [2]. Indeed, the backbone of medical treatment for both first line and recurrence is a platinum compound, being carboplatin the most frequently administered drug [2]. Patients that respond to platinum-based treatments have a better outcome and can be considered for maintenance treatment with PARP inhibitors (PARPi), orally available targeted drugs that impair the DNA repair mechanism [3].

Thirteen percent of OC patients harbor a deleterious germline mutation in Breast cancer gene 1 and 2 (BRCA1 and 2), that causes a defect in Homologous Recombination, an high-fidelity DNA repair mechanism [4]. These women tend to show huge response to both platinum first-line treatment and rechallenge, and are the best candidates for PARPi maintenance therapy [5, 6].

Although platinum compounds are overall well tolerated, one of the issues related to their administration is that they can induce hypersensitivity reactions (HSRs) in around one tenth of OC patients [7, 8] . Namely, HSRs to platinum salts seem to be both immunoglobulin type E (IgE) and T lymphocyte mediated allergies, and their manifestations are widely variable, ranging from mild toxicity to life-threatening events[9]. Although desensitization can be attempted, it is both time consuming and may elicit severe reactions, being not always feasible, particularly after a severe HSRs [9-12]. The difficulty of reintroducing platinum might affect the subsequent treatment options and eventually the general outcome.

The most important risk factor for HSRs is the cumulative exposure to platinum, although also a history of allergic reactions and a long interval between treatments or the type of scheme administered might concur [8, 9, 13, 14].

Moreover, Moon and colleagues[15] suggested that also BRCA mutation may play a major role, although data in literature are controversial [15-20].

Analysis of the incidence of HSRs according to BRCA status may have been jeopardized by several confounding factors, such as the longer lifetime platinum exposure of BRCA mutated women compared with wild type ones, the small number of patients in each cohort and the administration of prophylactic premedication [15-20].

For this reason, we conducted a multicenter retrospective study that aimed at evaluating the incidence and severity of HSRs to platinum compounds in patients with OC and known BRCA status. Moreover, we performed a systematic review of literature and a meta-analysis including all published studies evaluating the incidence of HSRs to platinum according to BRCA status in women with OC.

Materials and Methods

Study design

This is an observational, retrospective, multicenter clinical study including OC patients with a known BRCA status, treated between the beginning of 2003 and the end of 2019 in five Italian centers specialized in gynecologic oncology. The aim of the study was to characterize and describe patients with HSRs to platinum compounds and to describe which is the relationship between BRCA mutation and incidence and severity of HSRs in our cohort.

For all patients we recorded the following data: histology, type of surgery and first line therapy, BRCA status, number of total lines and cycles received (both platinum and non-platinum based), line and cycle of HSRs onset, symptoms, history of other allergies and if desensitization was attempted. We retrospectively graded the severity of HSRs according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. In order to describe the time to HSR during the platinum exposure, we calculated the total duration of exposure to platinum salts (in days), summing up the duration of all platinum lines received by the patients. This calculation does not take into account the platinum-free interval among subsequent lines.

Systematic review

We performed a systematic review of literature in February 2020 according to the PRISMA guidelines. We searched for available articles on Pubmed, evaluating the incidence and features of HSRs to platinum compounds in OC patients with known BRCA status. We used the MeSH keywords "hypersensitivity", "ovarian cancer", "BRCA", "allergic reaction" and "allergy". We also manually reviewed meeting abstracts presented at ASCO, ESMO and ESGO Meetings between 2016 and 2019. Two authors (G.G. and G.S.) independently performed the literature research and checked the relevance and appropriateness of the articles and abstracts included. We excluded case reports and included only studies in English. After the first selection, full-text articles and meeting abstracts were reviewed for all the studies included in the analysis. We directly contacted the first and last authors of the papers if data were unclear or not completely reported.

Statistical Analyses

Descriptive statistics were reported as absolute numbers and proportions, or as median and range for continuous variables. Patients were categorized in two groups according to BRCA status: BRCA wild type and BRCA mutated.

The two groups were compared in terms of: (i) proportion of any grade HSRs; (ii) proportion of severe HSRs; (iii) cumulative incidence over time of any grade HSRs; (iv) cumulative incidence over time of severe HSRs. Cumulative incidence of HSRs was calculated during the total duration of exposure to platinum salts. The Kaplan-Meier method was used to calculate the cumulative incidence of both any-grade HSRs and severe HSRs; the log rank test was used to compare the outcome of BRCA wild type and BRCA mutated patients.

In order to assess the role of BRCA status in terms of risk of HSRs, both univariate and multivariate analysis were conducted, using the Cox regression model. To perform multivariate analysis, in addition to BRCA status, we included history of other allergy (yes vs no), exposure to bevacizumab (yes vs no), exposure to pegylated lyposomal doxorubicin (PLD) (yes vs no). Both exposures to bevacizumab and PLD were treated as time-dependent covariates.

All statistical tests were two-tailed and P values less than 0.05 were considered statistically significant. Analyses were performed with IBM SPSS for Windows, Version 25.

For the meta-analysis, after data were abstracted from each included study, analysis was performed with the Review Manager [RevMan (Computer program). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.] software. For each included trial, the number of events (HSRs) was analyzed in BRCA wild type and BRCA mutated patients. Summary measure was odds ratio (with 95% CI). Statistical heterogeneity among the included studies was examined using the χ^2 test and the I^2 statistic. The latter statistic expresses the proportion of the total observed variability attributed to study heterogeneity. Due to the evidence of a significant heterogeneity, a random-effects model was applied.

Results

Retrospective cohort

432 patients with known BRCA status and a diagnosis of OC between 07 March 2003 and 15 September 2019, were recorded. Among these patients, 334 (77%) were BRCA wild type while 98 (23%) harbored a germline BRCA mutation [58 (13%) BRCA1 and 40 (9%) BRCA 2 mutated patients]. More than half of the patients (267 patients, 62%) had no family history of OC and Breast cancer (BC). Ninety patients (21%; 31 BRCA mutated and 59 BRCA wild type) had a second primary cancer, that was a BC in 48 cases. The patients were frequently diagnosed at an advanced Stage [FIGO Stage III and IV in 244 (56%) and 77 (18%) patients respectively] and with a high-grade serous histology (300 patients, 69%).

Most of the recorded women received an upfront surgery (251 patients, 58%). In around 60% of cases there was no residual disease (R0) after surgery. The most frequent first line treatment was carboplatin plus paclitaxel every three weeks (265 patients, 61%) followed by carboplatin plus paclitaxel and bevacizumab (113 patients, 26%). Median overall survival was 103 months in BRCA wild type population and 141 months in BRCA mutated cohort ($p<0.05$).

Baseline characteristics of study population are reported in Table 1.

Out of the 432 recorded patients, 409 were treated with at least one platinum-based line of therapy and were eligible for the analysis. Among them, 314 women were BRCA wild type (77%) and 95 were BRCA mutated (23%).

There was no statistical difference in median number of lines of therapy [1 (range 1-6) for BRCA wild type and 2 (range 1-6) for BRCA mutated patients ($p = 0.194$)] and median duration of exposure to platinum [126 (range 42-893) and 197 (range 42-896) days for BRCA wild type and mutated patients respectively ($p = 0.145$).

Overall, we recorded 46 (11%) HSRs. Among them, 26 (6% of patients) were severe (Grade 3 and 4) reactions. All HSRs to platinum salts were related to carboplatin.

Incidence of any grade HSRs was 29/314 (9%) among BRCA wild type patients, vs 17/95 (18%) among BRCA mutated patients (Odds ratio [OR] 2.14, 95% CI 1.12 – 4.10, $p= 0.02$). We observed a numerically higher incidence of severe HSRs in BRCA mutated patients, although the difference was not statistically significant (5% in BRCA wild type vs 11% in BRCA mutated cohort, OR 2.19, 95% CI 0.96 – 5.01, $p = 0.06$) (figure 1).

The risk to develop HSRs increases with duration of exposure to platinum, particularly in BRCA mutated patients. The cumulative incidence of any grade HSRs was 21% vs 23% after 12 months and 38% vs 60% after 18 months in BRCA wild type and BRCA mutated patients respectively (Hazard Ratio [HR] 1.72,95% CI 0.94 – 3.12, $p= 0.073$). This temporal trend was also observed in severe HSRs, although not statistically significant. Indeed, the cumulative incidence in severe HSRs was 11% vs 16% after 12 months and 27% vs 41% after 18 months in BRCA wild type and BRCA mutated patients respectively (HR 1.88, 95% CI 0.85 – 4.16, $p = 0.11$) (see figure 2).

These results were confirmed also at multivariable analysis, showing that harboring a germline BRCA mutation was related to a higher incidence of HSRs (HR: 1.84, 95% CI 1.00-3.99, p=0.05) while having received PLD was related to a lower incidence of HSRs (HR: 0.03 95% CI 0.004 – 0.22, p=0.001). There

was no statistical difference in HSRs incidence according to a previous history of allergy or treatment with bevacizumab.

Systematic review and Meta-analysis

We performed a meta-analysis including both previously published papers and our multicentric retrospective study.
A total of 429 papers were identified from Pubmed. After individuating the duplicates and excluding studies that did not meet inclusion criteria, we selected 4 full text studies. After manually reviewing the meetings proceedings we added further 2 abstracts to the analysis.

Characteristics of these studies are described in table 2. These studies were published between 2013 and 2018. All of them were retrospective analyses of patients treated either in clinical trials (1 study) or in clinical practice (5 studies). A total of 843 patients were included in the current meta-analysis. Among them, 281 were BRCA mutated and 562 were BRCA wild type. The largest study was our retrospective analysis, accounting for approximately 50% of the total number of patients. The incidence of HSRs varied largely both in BRCA mutated population and BRCA wild type one among the different studies (see figure 3).

In the meta-analysis a BRCA wild type status was related to a lower incidence of HSRs (OR 2.63 95% CI 1.10-6.30). Nevertheless, there was an evidence of a statistically significant heterogeneity among the seven studies ($p = 0.03$; $I^2 = 71\%$) that, according to sensitivity analysis, could not be explained excluding only one of them (See figure 4).

Discussion

In our series we found a higher incidence of HSRs to platinum compounds in OC patients harboring a BRCA mutation, not justified only by a longer exposure, while PLD was confirmed to be a protective factor also in our cohort. These data are strengthened by the meta-analysis we performed, including both our results and the ones from literature.

HSRs to platinum compounds have always been a challenging issue for medical oncologists and gynecologic oncologists. Indeed, they can be life threatening and their incidence is high, occurring in about one third of patients that have received more than 7 cycles of platinum [8, 10]. Although data on desensitization protocols and on prophylactic premedication suggest that they might reduce the incidence of both primary HSRs and recurrence after a first episode, they derive above all from retrospective series and are not conclusive neither consistent [9, 11, 16, 21, 22] .

On the other hand, platinum compounds are the main therapeutic resource in OC patients, being also the sine qua non for maintenance therapy with PARPi [3].

These issues highlight why it is essential to explore which are the most important risk factors for HSRs and if, on the other hand, there are any protective measures that can reduce the risk.

There is a strong agreement on the fundamental role of platinum exposure duration and on the cumulative dose of platinum in increasing the overall risk of HSRs; conversely, data on other factors like a long interval

between two platinum based treatments and a history of systemic allergic reactions, food allergy or atopy are less solid [8, 9, 17, 18].

A great deal of interest was risen in evaluating if BRCA status is a risk factor for HSRs but also in this setting, published results are contradictory [15-20].

Indeed, BRCA mutated patients are usually characterized by an increased sensitivity to platinum compounds due to their impaired DNA repair mechanism, receiving generally a higher number of cycles than BRCA wild type patients [6, 23]. This defective mechanism makes the cleavage of platinum–DNA adducts less effective, resulting in a better activity of these drugs but also in a higher production of these complex, that might elicit IgE mediated allergic reactions [15, 24].

To our knowledge, this is the largest study evaluating the incidence and risk factors for HSRs to platinum compounds in OC patients with a known BRCA status. It shows that BRCA mutated patients have a significantly higher risk to develop HSRs than BRCA wild type women, with a numerically higher percentage of severe HSRs. Moreover, the time to event curves show that the incidence of HSRs increases with cumulative exposure to platinum in BRCA mutated cohort more than in the wild type counterpart, suggesting that the higher probability to develop a HSRs is not related only to a longer exposure in BRCA patients but to intrinsic features of this population.

At a multivariable analysis, the only risk factor we have identified is BRCA mutation, although p value did not reach statistical significance (p= 0.05). On the contrary, receiving PLD was a strong protective factor in our cohort of patients.

This study should be compared with previous papers that focused on the same issue [15-20].
For this reason, we performed a meta-analysis that endorses our results, confirming that BRCA mutations are a risk factor for HSRs. Nevertheless, it highlights also that the studies included are highly heterogeneous (see figure 3, figure 4 and table 2).
Indeed, population characteristics and overall results vary broadly and this is emphasized by the difference in incidence of HSRs among the studies (figure 3).
For example, the first paper estimating the incidence of HSRs according to BRCA status was a monocentric retrospective analysis performed by Moon and colleagues[15] in a cohort of patients treated with a combination of carboplatin alone (AUC 3–5) plus oral Olaparib in the setting of two clinical trials [15]. It recruited 87 patients and among them 17% had a history of previous HSRs to carboplatin and 64% had BRCA mutation or a positive BRCAPro (55 and 1 patients respectively); median number of previous cycles was 9 (range 0–42) [15]. Thus, analyzed data came from a high-risk group, with a significant number of BRCA mutated, heavily pretreated patients. The overall incidence of HSRs in this population was 33%, but harboring a BRCA mutation massively increased the risk with an OR of 13.1 (p= 0.0017) [15]. These data were confirmed by Altwerger et al.[16], who also recruited a population with a long exposure to platinum compounds (at least 7 cycles) and enriched in BRCA mutated patients (44%), treated outside a clinical trial in a single institution [16].
On the other hand, in both the analyses from the Princess Margaret Cancer Centre and from the Istituto Nazionale Tumori - Fondazione “G. Pascale”, there was no difference in HSRs incidence according to BRCA status. Both studies recruited patients with a high number of previous carboplatin cycles but BRCA status was available for a low percentage of patients (about one fourth) [17, 18]. Specifically, the study from Jerzak et al.[17] evaluated 450 patients that had received at least 6 cycles of carboplatin, with the aim of estimating the preventive role of diphenhydramine prophylaxis. Although this study showed a low incidence of HSRs among these patients (2 out of 37) the small number and the possibility of confounding factors like having received a premedication do not let to draw a conclusion [17].

Lastly, both abstracts by Maccaroni et al.[20] and Garcia et al.[19] analyzed data from a small group of patients; unfortunately important risk factors, like the total duration of exposure to platinum compounds were not evaluated [19, 20].
Our study was the only multicentric retrospective study evaluating patients from everyday practice. It analyzed a large cohort of women with a known BRCA status and included also patients treated during the first line, for whom data from literature are scarce. Therefore, our cohort was less pretreated with a median number of 1 line of therapy but it reflects a real-life setting.
It has also the noteworthy quality of evaluating the incidence of HSRs according to the total duration of exposure, underlining that there is a far greater increase in the time-dependent risk in BRCA mutated patients. This is not in contrast with previous report suggesting an early onset of HSRs in BRCA mutated patients[15]. As a matter of fact, it highlights that the risk is increased over all the history of the disease and that it does not level off in heavily pretreated patients.

Finally, it suggests that the protective role of PLD could become a precious tool in these patients. The lower incidence of HSRs to carboplatin when administered with PLD has been evaluated thoroughly in previous papers and though the biological mechanism is not completely known, the antigens masking caused by PEGylation, the well-known role of doxorubicin on tumor microenviroment (TME) and eosinophils compartment and the PLD specific inhibition of both B cells activity and macrophages phagocytosis seems to be involved [13, 25-31] . Although data on PLD role are strongly concordant, most of these studies did not record BRCA status of patients and focused on a specific setting of treatment (above all the second line therapy) [13, 26, 31]. We suggest that the role of PLD is maintained in both BRCA mutated and BRCA wild type patients and over the time, having analyzed it as a time-dependent variable.

Our study has some drawbacks due to the retrospective nature, among them the most relevant ones are the missing data about the use of premedication and the fact that, due to the long period of recruitment, the cohort is heterogeneous. Moreover, mild reactions might have not been recorded, although we think that this is a minor limitation because the missing information is likely to be not clinically relevant and probably did not cause the discontinuation of platinum treatment. Lastly, we have few data on desensitization and a low number of these patients received PARPi though not reflecting the current therapeutic algorithm in OC.

In conclusion, our results consolidate the role of BRCA mutation as a risk factor for HSRs. This has relevant consequences in clinical practice. Indeed, the role of platinum-based treatments has become even more important in the current therapeutic algorithm for BRCA mutated patients, as a prelude to a PARPi maintenance treatment [3, 32, 33]. A careful consideration of the increased risk of HSRs in BRCA mutated patients can guarantee a better approach in terms of duration of the infusion, premedication, parameters checks and above all on the choice of the best platinum doublet [9]. Indeed, given the comparable efficacy with other combinations, the protective role of PLD should be considered in this category of patients, both in first line and above all at relapse [13, 34, 35].

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Disclosure

Patients characteristics	Overall		BRCA mutated		BRCA Wild type	
	N° of pts (median)	% (range)	N° of pts (median)	% (range)	N° of pts (median)	% (range)
Number of patients	432	100%	98	23%	334	77%
Median age at diagnosis (years)	62	(24-86)	56	(35-77)	64	(24-86)
BRCA mutation status						
BRCA 1	58	13%	58	59%	--	--
BRCA 2	40	9%	40	41%	--	--
Family History of BC or OC						
BC only	56	13%	20	20%	36	11%
OC only	15	3%	7	7%	8	2%
both BC and OC	18	4%	9	9%	9	3%
No history of BC or OC	267	62%	41	42%	226	68%
NA	76	18%	21	21%	55	16%
Second primary cancer						
yes	90	21%	31	32%	59	18%
no	321	74%	61	62%	260	78%
NA	21	5%	6	6%	15	4%
FIGO Stage at diagnosis						
I	47	11%	8	8%	39	12%
II	34	8%	9	9%	25	7%
III	244	56%	57	58%	187	56%
IV	77	18%	13	13%	64	19%
NA	30	7%	11	11%	19	6%
Histology						
Serous	310	72%	72	73%	238	71%
Endometrioid	41	9%	8	8%	33	10%
Clear cell	10	2%	3	3%	7	2%
Undifferentiated	31	7%	9	9%	22	7%
Mullerian	1	<1%	–	0%	1	<1%
Other	12	3%	–	0%	12	4%
NA	27	6%	6	6%	21	6%

Patients characteristics	Overall		BRCA mutated		BRCA Wild type	
	N° of pts (median)	% (range)	N° of pts (median)	% (range)	N° of pts (median)	% (range)
Grading						
G1	3	1%	--	0%	3	1%
G2	19	4%	3	3%	16	5%
G3	376	87%	90	92%	286	86%
NA	34	8%	5	5%	29	9%
Surgery during first line						
Upfront	251	58%	59	60%	192	57%
IDS	148	34%	34	35%	114	34%
Not received	20	5%	2	2%	18	5%
NA	13	3%	3	3%	10	3%
Residual disease after primary cytoreduction						
R0	263	61%	69	70%	194	58%
R1	70	16%	11	11%	59	18%
R2	41	9%	6	6%	35	10%
NA	25	6%	7	7%	18	5%
First line chemotherapy						
Carboplatin AUC 6/5 3w	11	3%	2	2%	9	3%
Carboplatin AUC 6/5+paclitaxel 175 mg/m^2 3w	265	61%	64	65%	201	60%
Carboplatin AUC 6+paclitaxel 175 mg/m^2+ bevacizumab 15 mg/kg 3w	113	26%	24	24%	89	27%
Carboplatin AUC2+ paclitaxel 60 mg/m^2 w	7	2%	--	0%	7	2%
Carboplatin AUC5+PLD 30 mg/m^2 3w	4	1%	3	3%	1	<1%
Carboplatin w	1	<1%	—	0%	1	<1%
NA	31	7%	5	5%	26	8%

Table 1: Baseline characteristics

Legend: AUC: Area under the curve, BC: Breast Cancer, BRCA mut: BRCA mutated, BRCA wt: BRCA: wild type, IDS : interval debulking surgery, NA: Not Available, OC: Ovarian Cancer, pts: patients , RO: no residual disease after surgery, R1:<1 cm of residual disease after surgery, R2:>1 cm of residual disease after surgery, w: weekly, 3w: every three weeks.

Study	Years	Eligible pts	Pts in clinical trial	Multicentric	BRCA mut	BRCA wt	HSRs	HSRs in BRCA mut	HSRs in BRCA wt	Median n° of platinum based cycles	% of G3/G4 reaction	Premedication	Ref
Moon et al (2013)	2008 - 2013	87	yes	no	56	31	29	27	2	9 (0-42)	28 (5 pts)	Only in pts with a history of mild-to-moderate HSR	[15]
Maccaroni et al (abs 2016)	2010 - 2015	27	no	no	14	13	10	9	1	NA	NA	NA	[20]
Bergamini et al (2017)	2007 - 2016	46	no	no	26	20	11	7	3	8 (3-17)	NA	NA	[18]
Altwerger et al (2018)	2006 - 2016	91	no	no	40	51	51	31	20	14 (100% pts> 7)	NA	NA	[16]
Garcia et al (abs 2018)	2012 - 2016	62	no	no	13	49	26	4	22	NA	39 (16pts)	NA	[19]
Jerzak et al (2018)	2006 - 2012	121	no	no	37	84	11	2	9	≥6	20 (8 pts)	Diphenhydramine prophylaxis in 291 patients (65%)	[17]
Giannone et al (2020)	2003 - 2019	409	no	yes	95	314	46	17	29	1(1-6)	6(26 pts)	NA	

Table 2: Main features of studies evaluating HSRs to platinum according to BRCA status in Ovarian cancer. Legend: abs: abstract, BRCA mut: BRCA mutated, BRCA wt: BRCA: wild type, NA: not available, pts: patients, Ref: reference.

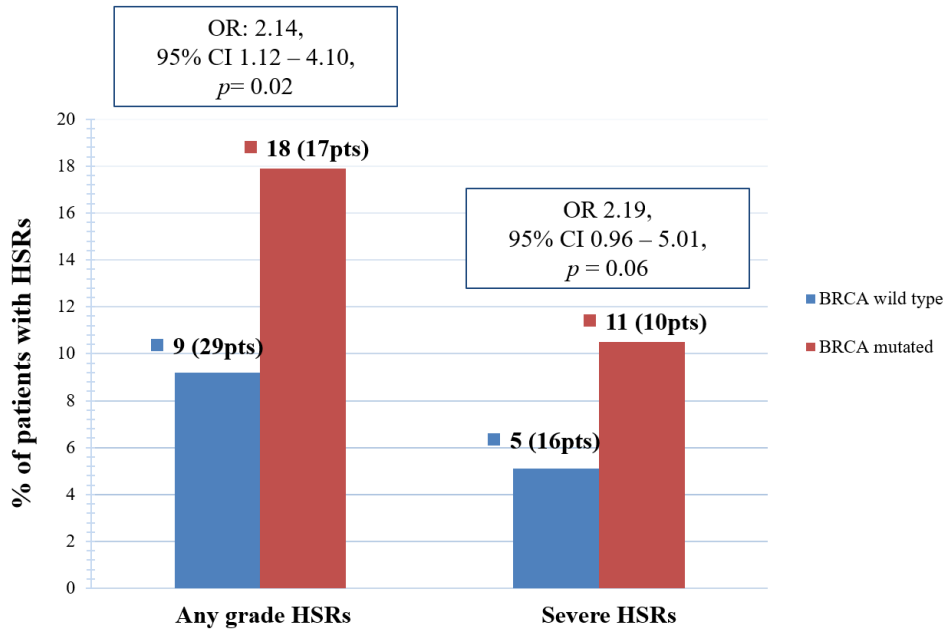
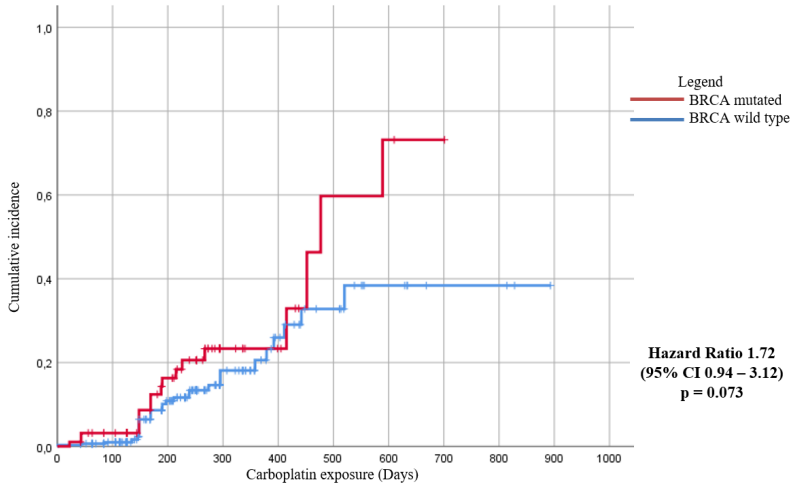


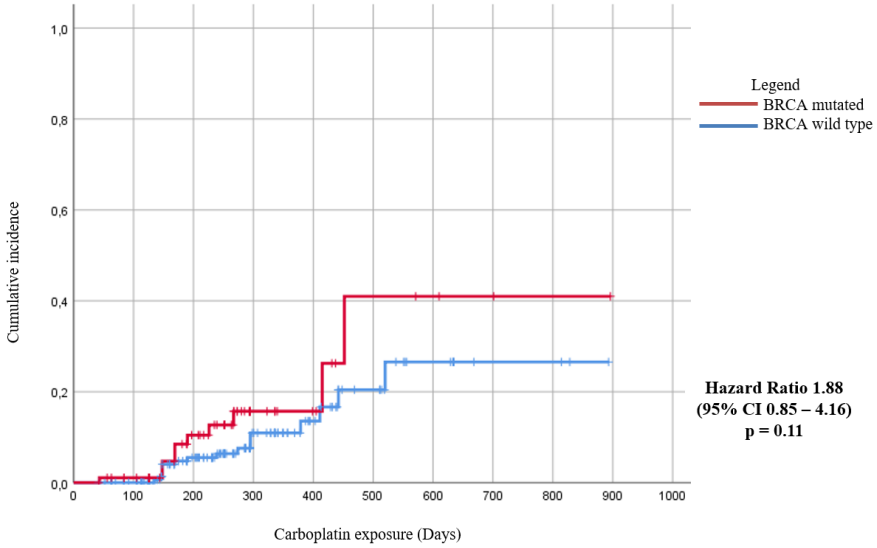
Figure 1: incidence of HSRs according to BRCA status.

Figure 2A



	N	Events	% at 12 months	% at 18 months
BRCAwt	314	29	21%	38%
BRCAmut	95	17	23%	60%

Figure 2B



	N	Events	% at 12 months	% at 18 months
BRCAwt	314	16	11%	27%
BRCAmut	95	10	16%	41%

Figure 2: Cumulative incidence of HSRs, any grade (Figure 2A) and severe (Figure 2B), according to duration of exposure (days) in BRCA mutated (BRCAmut) and BRCA wild type (BRCAwt) cohort.

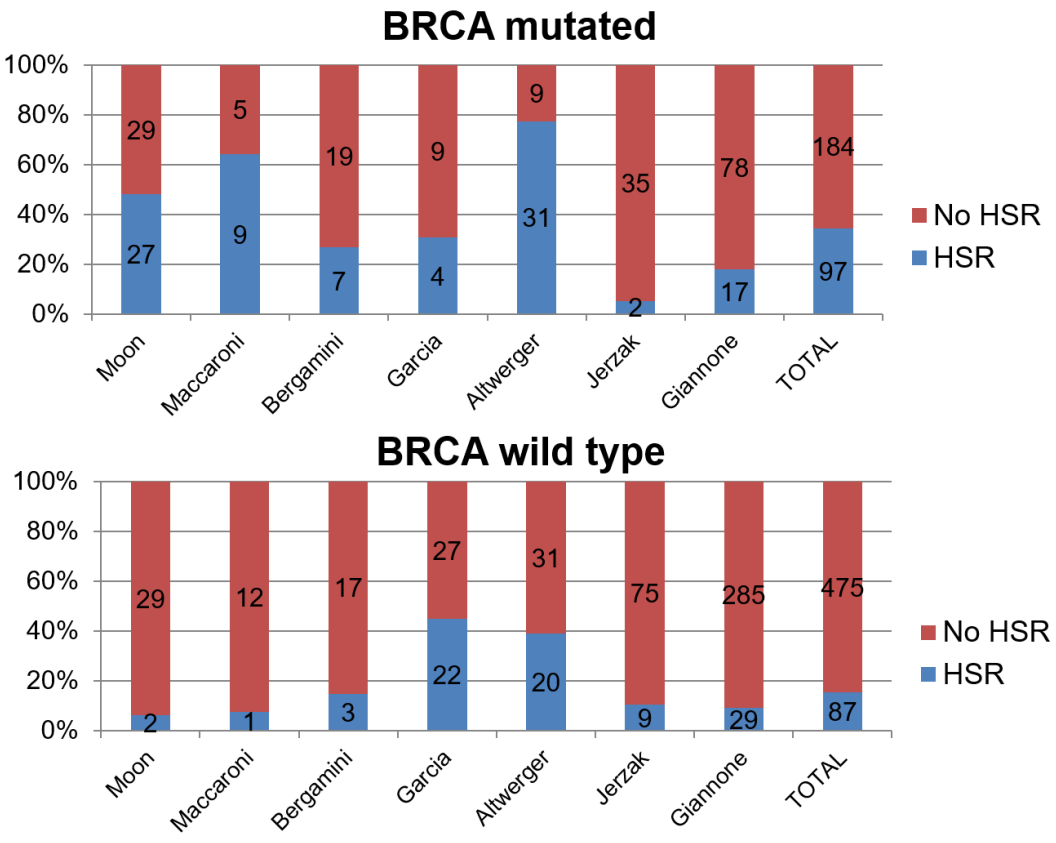


Figure 3: incidence of HSRs in BRCA mutated and BRCA wild type cohorts of each study included in the meta-analysis.

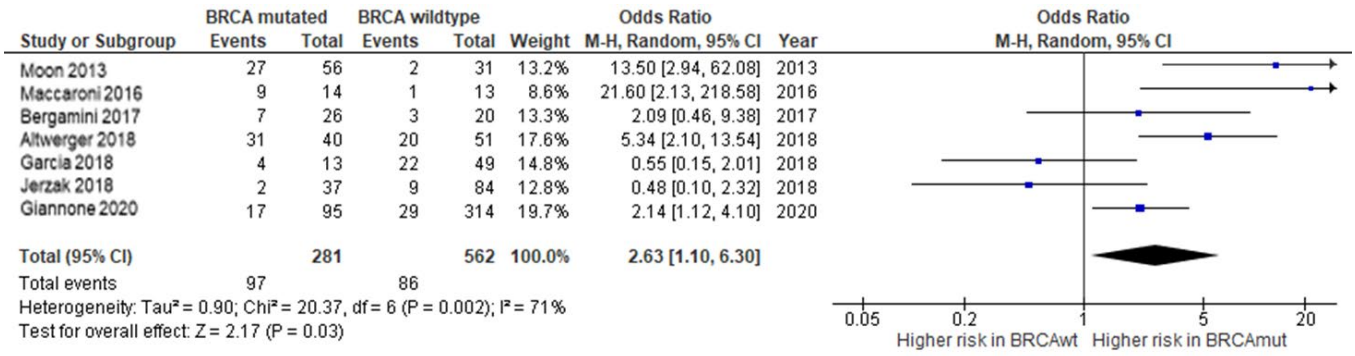


Figure 4: Hypersensitivity reaction to platinum derivatives according to BRCA status. Meta-analysis of published studies.

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