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REVIEW

A systematic literature review assessing if genetic biomarkers are predictors for platinum-based chemotherapy response in ovarian cancer patients

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Abstract

Background Ovarian cancer is the deadliest of gynecologic malignancies with the 5-year overall survival rate remaining at approximately 30%, a rate that has not improved over the last three decades. Standard of care for epithelial ovarian cancer patients consists of a platinum compound with a taxane given intravenously following debulking surgery; however, 80% of cases relapse within 2 years of diagnosis. This review sought to identify key underlying biomarkers related to platinum resistance in ovarian cancer to establish possible prognostic biomarkers of chemoresponse.

Methods A systematic literature review was conducted across three databases PubMed, EMBASE and SCOPUS to summarise the evidence for prognostic biomarkers in platinum-resistant ovarian cancer patients.

Results Forty-eight human studies were used in the review encompassing 6719 participants in retrospective and prospective study designs. A total of 68 biomarkers were reported that were significantly correlated with chemoresponse and/or survival reporting a p value less than or equal to 0.05.

Conclusion This review accentuates the pleiotropic phenotypic complexities related to the response to platinum therapy in ovarian cancer. A one-size-fits-all approach may be ineffective in a large portion of patients, emphasising the need for a whole system-based approach and personalised treatment strategies. Identifying key biomarkers to aid clinical decision-making is the first essential step in developing and appropriating therapies for at-risk patients, reducing toxicity and improving quality of life.

Keywords Platinum resistance · ovarian cancer · Chemoresistance · Prognostic biomarker

Introduction

Ovarian cancer was reported as the leading cause of gynaecological cancer death in Australia in 2016, and it is estimated that by 2035, global ovarian cancer deaths will increase by 67% [1, 2]. Although deemed highly curable if diagnosed in its early stages, 70% of cases are not diagnosed until cancer has reached an advanced stage [3]. The first-line treatment for this cancer is a combination of chemotherapy with a platinum and taxane agent [4]. Certain patients have been found to be resistant to platinum therapies and prognostic biomarkers may be predictive of chemotherapy response. To examine possible biomarkers, a systematic literature review was conducted on the published, peer-reviewed literature to identify potential key markers that support validation as predictive biomarkers for chemoresponse in ovarian cancer.

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Using stringent inclusion and exclusion criteria, examining patient selection, chemotherapy regimens, laboratory and statistical methodology, the authors identified forty-eight (48) high-quality human trials recruiting 6719 patients.

Background

Platinum-based drug therapy makes up the primary treatment protocol after surgical debulking for ovarian cancer; however, it is estimated that up to 20% of all ovarian cancer patients are intrinsically resistant to platinum-based therapies and up to 70% of first responders will go on to develop resistance and fatal disease [5, 6]. Platinum resistance poses a significant challenge to the clinical approach in affectively treating ovarian cancer patients. Since platinum therapy inception, very little advancement has been made in combating resistance in a population where 5-year overall survival is as low as 30% [7].

It has been suggested that genetic changes alone cannot sufficiently explain the complexities of chemotherapy resistance. Aberrant methylation, in this regard, has been recognised as one of the most common abnormalities associated with resistance in many cancer types, including ovarian cancer [3]. This review seeks to report the key biomarkers found to be correlated with platinum resistance in a wide variety of ovarian cancer histotypes, in an effort to identify potential prognostic markers for chemoresistance, advocating for personalised therapy in oncology.

Methods

Search strategy

The PICO (Population, Intervention, Comparison and Outcome) framework [8], search terms considered for inclusion, included "platinum resistance" AND "biomarkers" AND "methylation" AND "ovarian cancer" AND "human trial".

Due to a paucity of information regarding the review topic, the consensus was reached between the authors on the appropriate search strategy, based on preliminary searches of databases to ensure an adequate search return for a review. PubMed and SCOPUS searches were conducted using keywords ("platinum resistance" AND "ovarian cancer" AND "human trial"). EMBASE recognised "ovary cancer" rather than "ovarian cancer" and was subsequently included in the search using terms ("ovary cancer" AND "platinum" OR "carboplatin" OR "cisplatin" AND "resistance" AND "human trial"). Date selection filters were applied to screen papers published between 2000 and 10 October 2018.

Selection criteria

Papers were included if they covered predictive markers for platinum resistance and specifically, tumour markers prevalent in platinum resistance, published in English, in ovarian cancer patients regardless of debulking surgery who had received first-line platinum therapy. Peritoneal, ovarian, cervical and fallopian tube cancers were all included in the review due to the location and relationship of the histotypes in association with the review. Where papers included breast cancer or lung cancer with ovarian cancer in studies, these were also considered for inclusion in the review based on their prognostic significance to the review topic. Furthermore, research identifying predictive markers in relation to platinum and taxane combination therapies were considered for inclusion as being consistent with the research topic. The final inclusion criteria included observational retrospective or prospective studies that identified genetic markers in response to platinum-based chemotherapy in vivo.

Articles were excluded dependent on criteria based on treatments other than platinum therapy, animal carcinoma, cancer cell lines, in vitro testing, cancers other than ovarian, measures of metastasis and tumorigenesis, measures of immune activity, ovarian cancer risk, quality of life measures, editorial papers and commentaries, research assessing the efficacy of tumour debulking strategies and all other studies unrelated to the review topic. It was decided that in vitro studies would be excluded from the review as, although essential, the primary weakness of such studies is they fail to replicate the synergistic cellular conditions of a complex organism.

Critical appraisal

Rigorous appraisal of full-text articles was undertaken using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) tool [9]. The STROBE tool was selected as it is designed to provide a framework for cross-sectional observational studies to be reported on. Articles were assessed for a clear explanation of study design and methodology, patient eligibility criteria and sample selection methods. All outcomes, potential confounders and predictors were clearly defined, statistical and analytical methods explained and limitations unobtrusively discussed by the study authors. Follow-up time(s) should have been clearly stated and identification of how many participants completed each stage of the study, including the attrition rates. Funding, risk of bias and potential conflicts of interest were also assessed for each article included in the review in accordance with the STROBE checklist (Table 1).

Small sample size was a concern across 21 retrospective studies [10, 11, 20–22, 25, 26, 29–32, 40, 49–54, 58–62], whilst 4 studies were unable to compare markers across study cohorts [10, 15, 28, 47] or lacked a validation cohort

Table 1 Critical appraisal results: critical assessment of literature based on the STROBE checklist

Author/date	Title and abstract (1a) (1b)	Introduction (2) (3)	Methods (4) (5) (6) (7) (8) (9) (10) (11) (12A, B, C, D, E)	Results (13) (14) (15) (16) (17)	Discussion (18) (19) (20) (21)	Funding (22)	Total
Abdel-Fatah et al. (2014) [10]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A)	(13) (14) (15) (16)	(18) (19) (20)		17
Alanee et al. (2017) [11]	(1B)	(2) (3)	(4) (5) (6) (8) (12A) (12C)	(13) (14) (15) (16)	(18) (19) (20) (21)	(22)	18
Alsop et al. (2012) [12]	(1B)	(2) (3)	(4) (5) (6) (8) (9) (11) (12A) (12B) (12C)	(13) (14) (15) (16) (17)	(18) (20) (21)	(22)	21
Ayub et al. (2015) [13]	(1B)	(2) (3)	(5) (6) (7) (8) (11) (12A) (12B) (12C)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)	(22)	21
Chen et al. (2017) [14]	(1A) (1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (10) (11) (12A)	(13) (14) (15) (16)	(18) (19) (20) (21)	(22)	22
Despierre et al. (2014) [15]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (10) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)		21
Du et al. (2016) [16]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (12A)	(13) (14) (15) (16)	(18) (20)		15
Eitan et al. (2009) [17]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (12A) (12B)	(13) (14) (15) (16)	(18) (20)		16
Ferrandina et al. (2008) [18]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (20) (21)		20
Ferrandina et al. (2008) [19]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)		21
Ge et al. (2017) [20]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)	(22)	21
Helleman et al. (2006) [21]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B) (12D) (12E)	(13) (14) (15) (16) (17)	(18) (20) (21)	(22)	23
Heubner et al. (2010) [22]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (20) (21)		21
Iramaneerat et al. (2011) [23]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (20) (21)	(22)	22
Jin et al. (2015) [24]	(1A) (1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B) (12D) (12E)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)	(22)	25
Ju et al. (2016) [25]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B)	(13) (14) (15) (17)	(18) (20) (21)		19
Kang et al. (2006) [26]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)		20
Kucukgoz et al. (2014) [27]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (20) (21)		19
Kuhlmann et al. (2014) [28]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)	(22)	22
Makhija et al. (2003) [29]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (20) (21)		19
Marchini et al. (2013) [30]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (20) (21)		20
Mignogna et al. (2016) [31]	(1A) (1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)	(22)	24
Muallem et al. (2014) [32]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (10) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (20) (21)		21
Österberg et al. (2009) [33]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)		20
Palmieri et al. (2013) [34]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)	(22)	21
Pennington et al. (2014) [35]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)		22
Pylväs-Eerola et al. (2015) [36]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (20) (21)		19
Pylväs-Eerola et al. (2016) [37]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (20) (21)		20
Reimer et al. (2007) [38]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (20) (21)		21
Rubatt et al. (2012) [39]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (20) (21)		21
Saldivar et al. (2007) [40]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)		20
Sapoznik et al. (2017) [41]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)		21
Scalici et al. (2017) [42]	(1A) (1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (20) (21)	(22)	23
Scartozzi et al. (2003) [43]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (20)		18
Shehata et al. (2009) [44]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (20) (21)	(22)	20
Smith et al. (2007) [45]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (20) (21)		19
Sohn et al. (2012) [46]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (20)		19
Steffensen et al. (2014) [47]	(1A) (1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12D)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)	(22)	23

Table 1 (continued)

Author/date	Title and abstract (1a) (1b)	Introduction (2) (3)	Methods (4) (5) (6) (7) (8) (9) (10) (11) (12A, B, C, D, E)	Results (13) (14) (15) (16) (17)	Discussion (18) (19) (20) (21)	Funding (22)	Total
Steffensen et al. (2009) [48]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (20) (21)		20
Steffensen et al. (2008) [49]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)	(22)	23
Swisher et al. (2008) [50]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B)	(13) (15)	(18) (20)	(22)	17
Wang et al. (2013) [51]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)		21
Wang et al. (2017) [52]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (20) (21)	(22)	21
Wilczyński et al. (2017) [53]	(1A) (1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)	(22)	23
Wu et al. (2016) [54]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (20) (21)	(22)	22
Wysham et al. (2012) [55]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B) (12D)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)	(22)	23
Zhang et al. (2018) [56]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (9) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)	(22)	22
Zhao et al. (2016) [57]	(1B)	(2) (3)	(4) (5) (6) (7) (8) (11) (12A) (12B)	(13) (14) (15) (16) (17)	(18) (19) (20) (21)	(22)	21

(1A) Indicate the study's design with a commonly used term in the title or the abstract; (1B) Provide in the abstract an informative and balanced summary of what was done and what was found; (2) Explain the scientific background and rationale for the investigation being reported; (3) State-specific objectives, including any prespecified hypotheses; (4) Present key elements of study design early in the paper; (5) Describe the setting, locations and relevant dates, including periods of recruitment, exposure, follow-up and data collection; (6) Give the eligibility criteria, and the sources and methods of selection of participants. For matched studies, give matching criteria and the number of controls per case; (7) Clearly define all outcomes, exposures, predictors, potential confounders and effect modifiers. Give diagnostic criteria, if applicable; (8) For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group; (9) Describe any efforts to address potential sources of bias; (10) Explain how the study size was arrived at; (11) Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why; (12A) Describe all statistical methods, including those used to control for confounding; (12B) Describe any methods used to examine subgroups and interactions; (12C) Explain how missing data were addressed; (12D) If applicable, describe analytical methods taking account of sampling strategy; (12E) Describe any sensitivity analyses; (13) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up and analysed. Give reasons for non-participation at each stage; (14) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders. Summarise follow-up time (e.g. average and total amount); (15) Report numbers of outcome events or summary measures over time; (16) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included. If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period; (17) Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses; (18) Summarise key results with reference to study objectives; (19) Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias; (20) Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence; (21) Discuss the generalisability (external validity) of the study results; (22) Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

altogether [31]. Limitations in study design included lack of understanding of the mechanism of action for the biomarker was reported by 1 study [11] and another acknowledged the cutoff point for biomarker Ki67 in relation to the complexities of chemotherapy response and individuality of patient's [14]. Further limitations reported commonality of false positives [17], unknown oral contraceptive (OCP) use and its potential influence on exposure in the sample population [22], the use of metastatic tissue from alternate locations [30], heterogeneity of recurrence across paired comparisons [35], low biomarker expression in the chosen cohort [39], reliability and reliance of clinical data in medical records [40] and non-random selection [57].

Results

Literature selection

A total of one thousand one hundred one (1101) articles were identified in the initial database searches. PubMed ($n = 434$), EMBASE ($n = 268$) and SCOPUS ($n = 398$). Sixty-one duplicate titles were removed, leaving 1039 for screening. Title and abstract assessment constituted the removal of a total of 938 papers in three independent inspections to ensure confidence in article selection. Twenty-three full-text articles were removed due to their inappropriateness to the selection criteria, including four articles that were unable to be accessed in their full-text form. A total of 48 full-text articles were retained for review herein (Fig. 1).

Prospective cohort study characteristics and outcome measures

Of the studies included in this review, seven articles consisted of prospective study designs [12, 16, 18, 19, 24, 48], with one retrospective and prospective combination study [42] (Supplementary Table 2). A total of 1438 patients were selected with various stages of epithelial, peritoneal and fallopian tube cancers from Danish, Australian, Italian, Chinese and American populations. All but one study specified primary treatment protocol of a "standard" taxane and platinum therapy consisting of 75–100 mg/m^2 cisplatin OR area under the curve (AUC) 5 carboplatin plus paclitaxel 175 mg/m^2 3 weekly, for 6 to 8 cycles. All but one study conducted immunohistochemistry (IHC) of the selected biomarkers being studied [16, 18, 19, 24, 42, 48]. Alsop et al. [12] conducted a germline high-resolution melt analysis to explore biomarker breast cancer early onset gene (BRCA) 1 and 2 in treatment response.

Primary end points were varied across all groups, all covered platinum resistance as a common outcome, however, not as the primary outcome measure. Alsop et al. [12] and Steffensen et al.'s [48] outcome measures included overall survival (OS), progression-free survival (PFS) and platinum resistance (Pt-R). Du et al. [16] assessed OS and Pt-R, and Ferrandina et al. [18] assessed OS whilst also comparing Pt-R and platinum sensitivity (Pt-S) in their evaluation of the role of the recepteur d'origine nantais (RON) as a prognostic tool in ovarian cancer patients. Whereas in another study by Ferrandina et al. [19], topoisomerase-IIα (TOPO-IIα) assessed OS as a single measure. Jin et al. [24] on the other hand assessed PFS in their study on Annexin A3, and Scalici et al. [42] assessed PFS and OS as their primary end points in their combination retrospective and prospective study on serum and mesothelium vascular cell adhesion protein 1 (VCAM-1) expression in ovarian cancer patients versus healthy controls (Supplementary Table 2). Finally, the residual disease was established as an independent prognostic indicator across all studies.

Retrospective cohort study characteristics and outcome measures

Forty-one studies included in the review were of a retrospective design constituting the recruitment of 5281 patients with various stages of the ovarian, fallopian tube and peritoneal cancers (Supplementary Table 3).Twenty-five studies, representing 55% of enrolled participants in the retrospective trials, did not reveal the chemotherapy protocols received by patients; however, they consisted of at least one platinum-based therapy consistent with outcome measures [10, 11, 13–15, 17, 22, 25, 28–32, 35, 36, 38, 41, 44–46, 50–53, 58–60] and 6 studies included an unspecified taxane treatment with, or separate to platinum therapy [15, 21, 50, 57–59]. Ge et al. [20] reported patients received combinations of paclitaxel plus cisplatin or carboplatin, or cyclophosphamide plus Adriamycin® and cisplatin, for 6 cycles. Helleman et al. [21] reported the use of cisplatin or carboplatin plus cyclophosphamide or an unspecified "other" treatments. Rubatt et al. [39] compared intravenous (IV) or intraperitoneal (IP) cisplatin and paclitaxel therapies. Wang et al.'s [59] samples were treated with combinations of cisplatin; carboplatin; nedaplatin and paclitaxel or carboplatin; nedaplatin and docetaxel or nedaplatin and liposomal paclitaxel. And, Zhang et al.'s [56] patients were treated with cisplatin or carboplatin and paclitaxel or docetaxel 3 weekly for 6–8 cycles. Five studies used varying dosages of carboplatin (AUC4, 5, 6, 7.5 or 8) or cisplatin (75 mg/m^2) and paclitaxel (135–175 mg/m^2) over 6 cycles [26, 27, 40, 47, 58]. Steffensen et al. [49] reported patients were treated with AUC4 or 8 with 500 mg/m^2 cyclophosphamide, and Zhao et al [57] had patients on 135 mg/m^2 cisplatin on day 1 (d1) or 65 mg/m^2 taxotere d1 plus 30 mg cisplatin on day 2 (d2) to 4, or AUC4-6 carboplatin d2, 3 or 4 weekly for a minimum of 3 cycles.

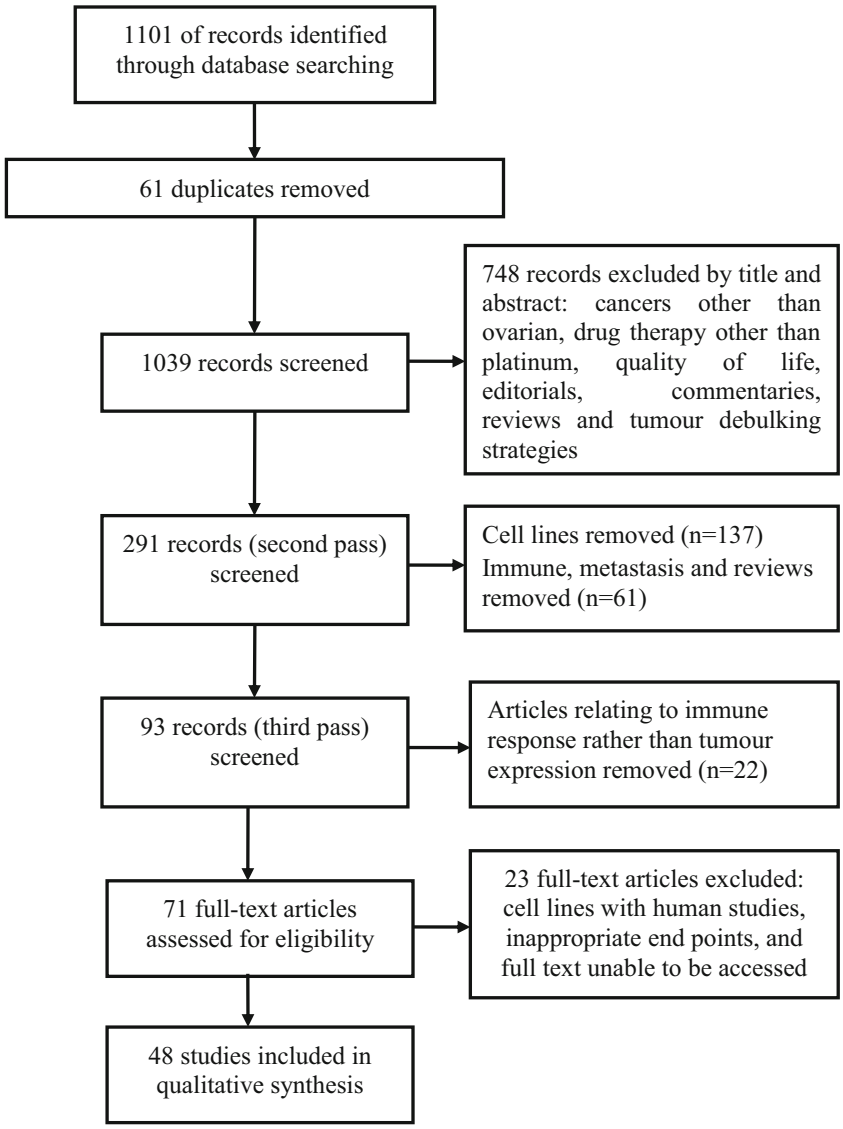

Fig. 1 PRISMA flow diagram: number of articles found at each point of the literature review search and selection point

Twenty-one studies used IHC to assess genetic data from tumours, whilst eleven studies used various polymerase chain reaction (PCR) techniques to assess target biomarkers. Two studies performed comparative genomic hybridisation (CGH) [20, 33] and two studies performed whole-exome sequencing [11, 46]. The remaining studies analysed ascites using flow cytometry [13], single-nucleotide polymorphism (SNP) array to assess protein kinase B (AKT1) [15], SNapShot array [26], fluorescence in situ hybridisation (FISH) alongside CGH [20], assessed peripheral blood for circulating tumour cells (CTC) using AdnaGen AG© [28], assessed serum protein and metabolite markers using enzyme-linked immunosorbent assay (ELISA) and Western blotting for protein detection, and nuclear magnetic resonance (NMR) for metabolite detection [54], and combined Western blotting with IHC for the assessment of platelet-derived growth factor D (PDGF-D) [56].

There was high heterogeneity in reference to clinical end points across all studies in the review including PFS, ovarian cancer-specific survival (OCSS), OS, platinum-free interval (PFI), time to relapse (TTR), response rate (RR), disease-free survival (DFS), clinicopathological parameters, Pt-R and Pt-S. Swisher et al. [50] also assessed secondary BRCA mutations in resistant patients aside from the aforementioned end points.

A total of 8197 markers, including but not limited to chromosomes, enzymes, kinases, proteins and genes, were screened resulting in 96 potential biomarkers for discussion (Supplementary Table 4). Twenty-one studies included a single candidate marker [14, 15, 17, 20, 22, 26, 31, 32, 39, 41, 44, 45, 49–51, 56, 57, 58–59]; two studies each reported 2 [35, 47], 4 [13, 30], 5 [34, 40], 6 [25, 37] and 7 [10, 55] biomarkers; four studies reported 3 [11, 23, 27, 28] and the

remaining studies reported 8 [38], 9 [21], 10 [33], 11 [54] and 15 [29] markers respectively.

Biomarkers associated with platinum resistance

Excision repair cross-complementation group 1 (ERCC1) was examined in two prospective studies, constituting 194 participants [16, 48]. Du et al. [16] selected participants aged between 21 and 29 years. Twenty-nine samples were classified stage I, nine stage II, thirty-five stage III and nineteen stage IV from ninety-two patients. It was established that high ERCC1 expression in ovarian cancer may be associated with Pt-R but not OS and that response rate cannot be translated into survival. Positive ERCC1 expression was found in 75% of Pt-R patients compared with negative expression in 26.7% of Pt-R participants. Positive expression was furthermore associated with poorer PFS ($p = 0.0012$) compared with ERCC1-negative tumours, with a trend towards reduced survival in ERCC1-positive tumours; however, results were not statistically significant ($p = 0.099$).

Eighteen epithelial ovarian cancer patients and 6 controls were prospectively assessed for serum (sVCAM-1) and mesothelium VCAM-1 expression by Scalici et al. [42]. Positive mesothelium VCAM-1 expression was associated with Pt-R ($p = 0.052$) and negatively associated with OS and PFS, although not significantly.

Of the biomarkers assessed, ERCC1 was the most common, appearing in eight retrospective studies [25, 26, 28, 32, 39, 45, 48, 49]. ERCC1 C/C genotype was found to have a positive association with Pt-R but not OS, whereas the C/T and T/T genotypes were associated with a reduced risk of Pt-R [26, 49]. This finding was confirmed by Smith et al. [45] who found the C/C genotype had an increased risk of disease progression ($p = 0.051$) and death ($p = 0.033$) compared with C/T and T/T genotypes given platinum only versus platinum and taxane therapy. Similarly, all patients exhibiting higher ERCC1 expression were associated with an increased risk of progression when given platinum therapy only ($p = 0.003$) [45]. Patients given platinum and taxane combinations showed no significant differences in outcome measures across all genotypes in the same study. Steffensen et al. [47] also found ERCC1 expression to be positively associated with early relapse and Pt-R in their training set ($p = 0.0004$). CTC that were ERCC1 positive were reported as an independent predictor for Pt-R ($p = 0.015$) with a threshold greater than 0.2 ng/μL [28]. Muallem et al. [32] and Rubatt et al. [39] on the other hand found no statistical significance between expression and chemoresistance despite OS being reported as better in non-responders with low or intermediate ERCC1 scores [32].

Biomarkers significantly associated with Pt-R in the remaining retrospective studies included reduced expression of protein Ki67 in three independent studies [10, 14, 27], DNA-dependent protein kinase catalytic subunit (DNA-PKcs) and Rad3-related protein (ATR) expressing tumours combined with positive X-ray repair cross-complementing protein 1 (XRCC1) positive expression [10]. Elevated aldehyde dehydrogenase 1 (ALDH1) cancer stem cells [13], negative cluster differentiation (CD) 44 expression with positive ALDH1 expression [], survivin [25, 27], higher beclin 1 autophagy-related protein expression [25], single-nuclear variant (SNV) rs79419059 in nuclear pore gene (Nup) 107 [11], elevated expression of serine/threonine kinase 6 (STK6), also known as Aurora Kinase A (AURKA) [21, 31], higher microRNA (miRNA) Hsa-miR-199a-3p and Hsa-miR-27a [17] and polymorphisms in cytochrome P450 enzyme, CYP1A1 Ile462 Val [22], were all reported to be associated with Pt-R. Furthermore, the upregulation of miR-141 and miR-200c alongside BMP and activin membrane-bound inhibitor (BAMBI) was found to be associated with Pt-R in epithelial ovarian cancer (EOC) samples ($p = 0.005$, $p = 0.002$ and $p \leq 0.001$ respectively) [30]. In a study of SNP, D6S1581 was the only marker significantly related to Pt-R ($p = 0.0410$) [29], and 70% of relapsed EOC patients exhibited upregulation of the transforming growth factor-beta receptor 2 (TGFBR2) pathway [30].

There were five regions at chromosomal location 1q25.1-q41, containing G protein-coupled receptor family and genes involved in Ras signalling pathways, exhibited statistically significant alterations between sensitive and resistant tumours in thirty-two EOC patients []. Likewise, defining it as an independent prognostic factor, intense PDGF-D protein expression was observed in Pt-R tumours versus Pt-S ones and was associated with reduced DFS and OS [56].

Helleman et al. [21] reported a 9 gene set including STK6/AURKA along with fibronectin-1 (FN1) protein, proliferating cell nuclear antigen (PCNA), laminar B receptor (LBR), argininosuccinate synthase (ASS), collagen type 3 alpha 1 (COL3A1), sphingosine-1-phosphate phosphatase 1 (SGPP1) and integrin alpha E (ITGAE) and were able to differentially discriminate between non-responders and responders in tumours of their discovery set and may be an independent predictor of resistance with the advanced disease according to the FIGO stage. Wu et al. (2016) also observed differences in serum FN1 expression in combination with serpin family A member 1 (SERPINA1) and orosomucoid 1 (ORM1) upregulation as associated with Pt-R in a data set of 64 proteins. ORM1 was reported to be a more sensitive marker compared with FN1 and SERPINA1 when determining between Pt-S and Pt-R. Glutathione peroxidase 3 (GPX3) gene, on the other hand, was downregulated in Pt-R versus Pt-S samples [54].

High levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG) were associated with Pt-R, OS and poor DFS ($p = 0.002$, $p = 0.019$ and $p = 0.020$ respectively) []. Moreover, antioxidant enzyme peroxiredoxin 3 (PRXIII) was found to be expressed at higher levels in Pt-R compared with the Pt-S

group ($p \leq 0.001$); however, there was no significant correlation between OS and chemoresistance [51].

Biomarkers associated with overall survival

One hundred nine cases of stage III and fourteen cases of stage IV ovarian cancer patients were recruited from the Catholic University of Campobasso in Rome; the remaining eighteen cases recruited were undefined by the study [18]. One hundred three out of 141 advanced ovarian cancer cases were RON positive with the level of expression unrelated to any clinicopathological parameters examined. There was no association between relative risk of progression and the percentage of positive RON expression. However, higher RON expression was associated with shorter OS in Pt-R tumours compared with lower levels. The most significant association was observed at greater than 20% expression compared with cases below the subsequently defined cutoff point ($p = 0.024$). The authors felt by establishing a 20% cutoff point (as related to the risk of death) reduced bias, by removing an arbitrary reference point.

Ferrandina et al. [19] recruited 96 patients from the Gynecologic Oncology Unit of the Catholic University of Campobasso and Rome aged between 27 and 80 years, seventy-seven of which with stage III primary untreated ovarian cancer and nineteen with stage IV disease. Chemotherapy response was assessed according to the World Health Organisation (WHO) criteria and TOPO-IIα expression was assessed by IHC. Expression greater than 25% was associated with shorter OS and may be an indicator of intrinsic-biological aggressiveness in tumour cells rather than a marker of Pt-R itself.

Reduced OS was correlated with serine-threonine protein kinase (AKT1) amplification at chromosome 14q,32.33 [15], reduced human leukocyte antigen (HLA) class 1 expression [44], miR-146a expression [58], high steroid receptor coactivator-3 (SRC3) [34] and haematopoietic PBX-interacting protein (HPIP) expression [59].

Loss of MutL homolog 1 (*h*MLH1) gene expression was found to be an independent prognostic marker of improved OS ($p = 0.0065$) but not platinum responsiveness in stage III and IV EOC []. Reduced methylation of long interspersed repetitive sequence 1 (LINE-1) was found in patients with advanced stage disease and continued to reduce as cancer progressed []. Oestrogen receptor alpha (ERα) expression was identified as an independent prognostic factor, with levels being significantly higher in later stage III and IV disease ($p = 0.031$). And, human epithelial growth factor receptor 2 (HER2) was also significantly correlated with SRC3 expression, although no prognostic significance was reported in this regard ($p \leq 0.001$) [34].

Platinum sensitivity was able to be predicted in tumours expressing E2F1 to E2F7 ratios below cutoff point 2.08 (as determined by the difference between OS and DFS between groups) [38]. Higher E2F7 expression was predictive of longer DFS and OS ($p = 0.048$ and $p = 0.042$ respectively), whereas lower E2F7 expression was observed in refractory and resistant disease. Higher E2F1 and E2F2 expression, on the other hand, indicated significantly shorter DFS and OS in comparison. Conversely, higher E2F4 expression was identified as an independent predictor of favourable OS.

Biomarkers associated with platinum sensitivity

On the other hand, biomarkers associated with Pt-S tumours included Nup188 and 214 mutations [11], higher rates of scaffold protein p62, whereas high-mobility group box 1 (HMGB1) protein was comparable across both groups in the same study [25], losses in chromosomal regions 17q24.1 and Xq21.33-q22 [15], higher Hsa-miR-378 and Hsa-miR-449b expression [17] and neurotrophic tyrosine kinase receptor type 3 (NTKR3) amplification (defined as greater than 30% signal from all cells) [20].

Biomarkers with varied results

Jin et al. [24] challenged the sensitivity of Annexin A3 as a prognostic biomarker, due to the excretion of the protein by healthy human cells as well as tumour cells. In two trials, tissue samples were assessed by authors without prior knowledge of clinical parameters, such as tumour staging, grade and participant age [18, 19]. And in a third trial, IHC was independently evaluated by blinded observers who had no prior knowledge of clinical data [24].

Alsop et al. [12] recruited women aged 18 to 80, with newly diagnosed epithelial, peritoneal and fallopian tube cancers. Tumour DNA samples were screened for mutations in the BRCA1 and 2 exons. BRCA1 and 2 germline mutations are almost exclusively related to high-grade serous carcinomas (HGSC). Of the 1001 epithelial, peritoneal and fallopian tube cancers, patients carrying BRCA1/2 mutations were reported to be less likely to have disease progression within 6 months of completing first-line treatment ($p \leq 0.0001$). Response rates to second-line treatment were higher in carriers of mutations, however, without statistical significance ($p = 0.07$).

BRCA expression was the second most researched biomarker reported in four retrospective studies [25, 35, 50, 55]. Both germline and somatic loss-of-function mutation in BRCA along with Fanconi anaemia (FA) pathways predict higher RR to platinum therapy and improved OS [35]. BRCA1 presence was independent of age, pathological type of tumour, differentiation and federation of gynaecology and obstetrics (FIGO) score, and significantly lower expression was found in Pt-S versus Pt-R samples ($p \leq 0.05$) [25]. Swisher et al. [50] found that BRCA1 expression was absent in primary tumours but present in recurrent ones in two

samples, indicating a genetic reversion to wild-type mutation which may mediate chemoresistance in mutated ovarian cancers. And, Wysham et al. [55] conversely found no significant association between BRCA1 expression and clinical outcome. In the same study, however, Wysham et al. [55] reported a higher risk of recurrence which was associated with higher expression of 3 proteins, poly ADP ribose polymerase (PARP), Fanconi anaemia complementation group D2 (FANCD2) and tumour protein 53 (p53) in Pt-R patients.

Increased nuclear factor erythroid 2-related factor 2 (NRF2) was "borderline" significantly associated with chemosensitivity ($p = 0.056$) and, as part of the same antioxidant signalling pathway, increased Kelch-like ECH-associated protein-1 (KEAP1) expression post-therapy versus diagnosis was found to be associated with higher tumour stage only ($p = 0.0001$) [].

Although there were some significant associations between xeroderma pigmentosum (XP) D and XPG polymorphisms and OS, there were no statistically significant prognostic associations found for biomarkers; polarity protein (PAR6); paired box gene (PAX2); cyclin E1 (CCNE1); tau protein; protein deglycase (DJ1/PARK7); major vault protein (MVP) rs1057451 and rs4788186; phosphatase and tensin homolog (PTEN); H2A histone family member X (H2AX) [55], CD24, CD117 and CD133 [13] and XP gene polymorphisms in regard to chemoresponse. TOPO-IIα and ataxia telangiectasia mutated (ATM) gene were both assessed in two retrospective trials with conflicting results [26, 36, 45]. And of all 6921 somatically mutated genes in the study by Sohn et al. [46], none specifically discriminated between Pt-R and Pt-S groups despite hypermutations in HGSOC being independently associated with Pt-S and OS ($p = 0.002$ and $p = 0.012$ respectively).

Discussion

A review of the current literature reveals a large number of biomarkers related to platinum therapy response in ovarian cancer patients and some of these biomarkers may be used as prognostic indicators. It is further revealed that methylation and histone modifications may play a role in the association with biomarkers, such as BRCA1, *h*MLH1 and LINE-1, chemoresponse and subsequently clinical outcome. Moreover, epigenetic changes in these biomarkers may contribute to the relationship between biomarker and RR, as well as variability in individual responses to therapy [6].

Epigenetic regulation of DNA in cancer includes DNA methylation of CpG islands and histone modifications, changes in genetic behaviour without altering the sequence of DNA [58]. Since genetic alterations are nearly impossible to correct, epigenetic modifications in cancer make them the target for prevention and/or treatment strategies.

Methylation

Antitumour activity of platinum compounds is dependent on the platination of DNA strands, causing intra- and inter-strand breaks, leading to p53-initiated apoptosis [59].

Aberrant DNA methylation has been cited as a contributor to platinum resistance in ovarian cancer. Two epigenetic phenomena have been described: firstly that a global decrease in DNA methylation of heterochromatin leads to demethylation of several oncogenes, promoting tumorigenesis and secondly, more specific CpG island hypermethylation of tumour suppressor genes correlates to a loss-of-function in these areas [3, 60]. There is also some evidence to show that methylation changes may contribute to the acquired resistance to other chemotherapeutics and cancer types, including but not limited to melanomas and lung cancers, and including resistance to modern generation immunotherapies [61–64].

Furthermore, inhibition of drug-transporter pathways has been shown to resensitise tumours to platinum drug therapy. The demethylation of the folate-binding gene (FBP) in cisplatin-resistant (CP-r) cell lines initiates the reuptake of carboplatin (a second-generation platinum compound) [65]. This is also illustrated by the introduction of PARP inhibitors in BRCA-mutated genes. PARP inhibition reinduces cellular instability in cancer cells, leading to apoptosis [66]. The hypermethylation of BRCA1 results in the deactivation of homologous repair (HR) pathways, resulting in the disorderly behaviour of neoplasms [67].

Despite only one article in this review discussing methylation in regard to platinum response and OS, literature to date has reported BRCA1 inactivation by hypermethylation in the promoter region, rather than by somatic mutations, as observed by Pennington et al. [35], as being correlated with sporadic ovarian tumorigenesis [68]. Supporting the notion that genetic changes alone cannot account for the complexities of platinum resistance. That changes in nearly every mechanism related to cell survival are observed (Fig. 2), further necessitating the role of personalised therapy in oncology and in particular prognostic tools for the drug-therapy response.

Upregulation of nucleotide excision repair (NER) pathways has been reported as a participatory factor in the removal of platinum adducts[1] in cancer cells, promoting platinum resistance [70]. ERCC1 protein methylation was associated with Pt-S in human glioma cell lines. Active demethylation of ERCC1 further improved cytotoxicity of cisplatin [71]. In phase III clinical trial, ERCC1 expression was quantified in non-small cell lung cancer (NSCLC) before treating patients with one of two arms of chemotherapy. High ERCC1-expressing tumours were treated with docetaxel and gemcitabine and those with low expression were treated with docetaxel and cisplatin. Overall RR was assessed,

[1] DNA adducts are a piece of DNA bound to a chemical. In this instance, platinum drug becomes incorporated into the DNA as an adduct, thus being referred to as a platinum adduct [69].

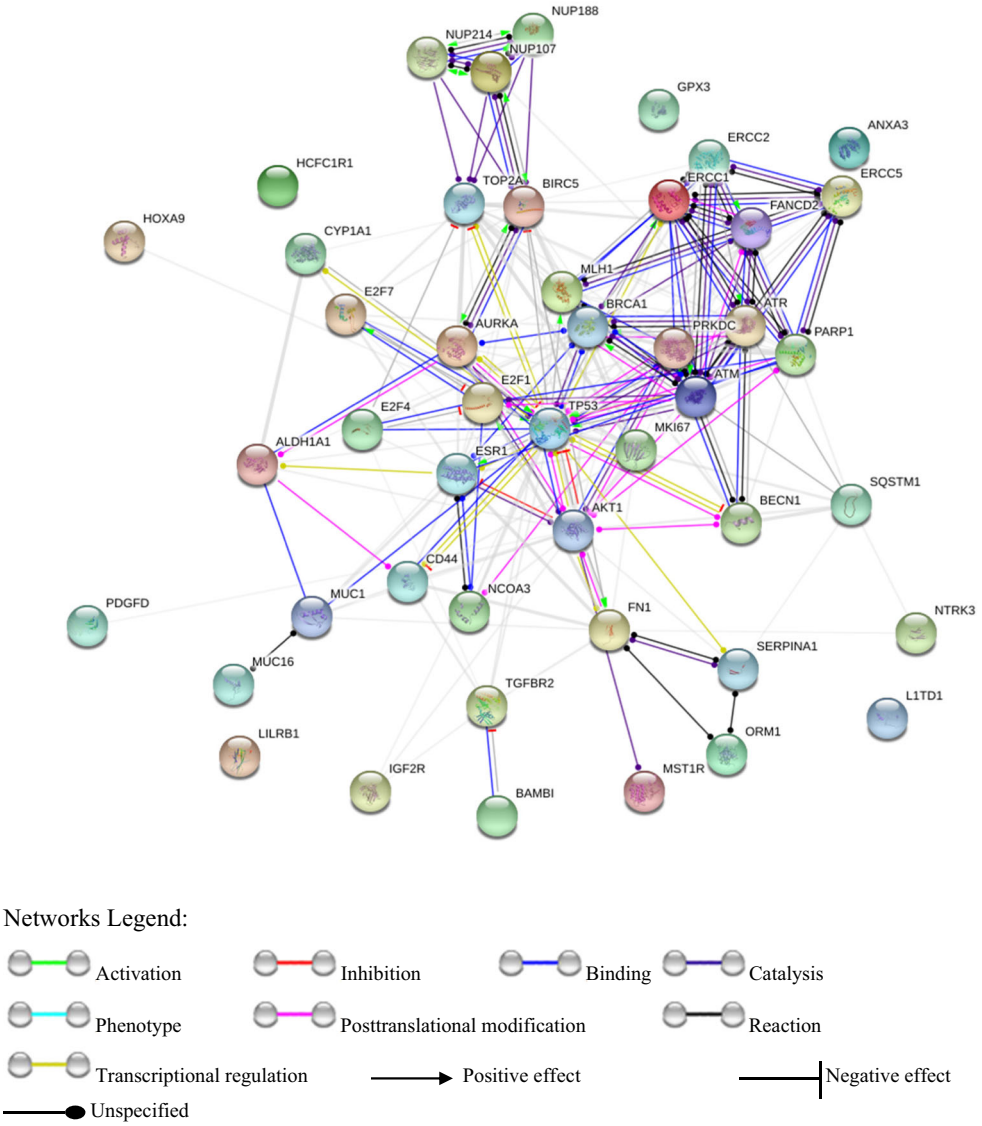

Fig. 2 Gene and protein interactions diagram: string diagram of protein and gene interactions found to have an association between platinum response and/or survival in ovarian cancer within this systematic review

revealing ERCC1 expression to be predictive of platinum response, consistent with the results found in our review [72].

ALDH1-positive breast cancer tumours were less methylated than positive ones; HER_2-positive subtypes also contained lower methylation frequencies at CpG islands, whereas ER-positive tumours contained higher methylation frequencies in the same gene set and may be used as predictive indicators for chemoresponse [73]. Our results failed to show a correlation with HER_2 and ERα and prognosis, however, did find that ALDH1-positive ovarian cancers may be predictive of Pt-R. Furthermore, Watanabe et al. [74] have reported that responsiveness to chemotherapy in EOC was associated with *h*MLH1 methylation in acquired resistance. *h*MLH1 was absent in primary tumours and secondary tumours showed a shift from unmethylated to methylated, excluding it from being associated with intrinsic resistance. Our review showed a significant correlation with OS, but not with chemoresponse in this instance.

Hypermethylation of KEAP1 lowers expression, increasing NRF2 expression, in the context of cancer this has been reported as a mark of drug resistance and disease progression [75]. Progressive hypomethylation of LINE-1 has also been associated with carcinogenesis in a broad panel of malignancies, consistent with the results found here although not significantly correlated to platinum responsiveness [, 76].

Research conducted by Li et al. [60] has identified three specific pathways downregulated by hypermethylation in ovarian cancer cell lines after 5 rounds of cisplatin treatment. These included fifty-five genes within cell adhesion molecules (CAMs), tight junction, peroxisome proliferator-activated receptor (PPAR) signalling and leukocyte transendothelial migration pathways. Hypomethylation and upregulated pathways were also identified including genes PIK3R3 (phosphoinositide-3-kinase regulatory subunit 3), PDGFRA (platelet-derived growth factor receptor alpha), E2F1,

TGFBR2, all signal transduction regulators associated with PI3K/Akt and cell cycle progression pathways which are also associated with other cancer cell types including glioma, melanoma, prostate, colorectal and pancreatic cancers. Furthermore, Yan et al. [77] observed hypermethylation in twenty of twenty-six genes, and hypomethylation in the remaining six genes, indicating that hypermethylation appears to be the main pathway associated with drug resistance to paclitaxel and cisplatin amongst at least 12 biological processes.

Guadecitabine (SGI-110) a next-generation hypomethylating agent has been shown to promote treatment-induced hypomethylation of tumour suppressor genes in tumour tissue samples during a multi-centre non-randomised phase I trial in combination with carboplatin, in heavily pre-treated platinum-resistant ovarian cancer patients. Induced re-expression of tumour suppressor genes or proapoptotic genes epigenetically silenced in resistant cells was reported, permitting a response to chemotherapy that had been previously lost [78]. Further substantiating the important role methylation may play in drug resistance, albeit to an unknown extent at this stage.

The methyl group bound to the cytosine molecule, which precedes the guanine molecule in CpG islands, is provided through the homocysteine cycle which is further generated from methionine by the MTHFR enzyme. The one-carbon transfer reaction begins with the adequate supply of substrate folate, which contains the essential one-carbon group used to methylate DNA [79]. Dixon et al. [80] reported a significant survival advantage in ovarian cancer patients with a synonymous C117T polymorphism reported as MTHFR SNP rs2066470 ($p = 0.03$); however, survival was not discussed in terms of platinum response. The further essential role of p53-mediated apoptosis is determinant on adequate zinc availability to the protein. Metallothionein, a heavy metal-binding protein generated from homocysteine through the transsulfuration pathway, removes zinc from p53, inactivating the protein allowing for a reduction in the appropriately programmed cell death [81, 82]. Elevated levels of this detoxification product of the methylation cycle have also been shown to be implicated in platinum resistance [65].

Copy number alterations

It has long been reported that copy number alterations (CNA) have been associated with response to platinum-based therapies, which involve large gains or losses of DNA resulting in the activation of oncogenes or the inactivation of tumour suppressors [83]. CNAs have been reported to be adaptive, aimed at providing some protection to metabolic or toxic challenges [84]. In cancer, focal amplifications can result in alterations of drug response; however, it remains unclear whether this is stochastic or directed in response to therapeutic burden [85]. It has also been written that "many CNAs and DNA methylations have been identified and been associated with carcinogenesis and cancer progression [86]. However, it remains challenging to pinpoint diagnostic, prognostic and therapeutic targets from this long list of cancer-associated genes" [83] further highlighting the complexities of platinum response in ovarian cancer.

Of biomarkers in this review, AKT1 amplification on chromosome 14q32.33, as one example, were significantly associated with reduced OS, PFS, PFI and Pt-R [15]. Song et al. [83] suggest that AKT1 is a key hub node, which interacts with a large number of other cascade CNAs, including but not limited to those within this review, Ki67 and peroxiredoxins. Pharmaceutical inhibition of bromodomain and extra-terminal (BET) family of proteins, including BRD4, which is also influenced by AKT1, when used in combination with PARP inhibitor olaparib, has been reported to sensitise triple-negative breast cancer cells to platinum salts in BRCA1 wild types and hinders homologous recombination-related member FANCD2 [87]. Furthermore, CCNE1 copy changes have been shown to benefit from CDK4 inhibitory drugs in ovarian cancer, of which ribociclib on its own or in combination with cisplatin has been shown to improve cell cycle arrest, restricting disease growth in vivo [88].

Heterogeneity of results

Variabilities in treatment protocols, study end points, sample sizes and consistency of definitions produced a highly diverse review. A lack of uniformity in regard to response to "chemotherapy" raises the question of whether the determined biomarkers are in fact predictive of platinum response or whether the interference of adjuvant treatment protocols complicates the outcome. Du et al. [16] acknowledge that the response rate is not reflective of survival and that each outcome should be measured independently to one another. And, the loss of effect with the addition of adjunct therapy was exclusively recognised by Palmieri et al. [34].

Platinum resistance should be treated as a primary outcome measure if the purpose of a trial is to assess chemoresponse, as responsiveness in particular does not translate to survival. It is difficult to draw conclusions from such a broad range of treatment regimens and biomarkers. Without sufficient controls treated solely with platinum therapies, it is problematic to assess platinum response if there is adjuvant therapy applied. However, in respect of ethical practice, it would be both impractical and unscrupulous to specifically deny adjuvant therapy to participants on the grounds of confounders.

What can be said of this review, nonetheless is the key significance of epigenetics in oncology, playing a role in both carcinogenesis and prognosis, highlighting the individuality of responsiveness. Larger, more consistent studies expressly assessing response to platinum therapy in ovarian cancer,

involving key cellular pathways and the role of methylation of key genes implicated in the pathways outlined in the literature, are essential to be able to confidently develop prognostic tools for clinicians in the future.

Conclusions

Few substantial conclusions can be drawn from a review of studies featuring significant heterogeneity in varying treatment protocols, sample sizes and populations, arbitrary cutoff points in regard to relatability and generalisability, and variability of outcome measures.

The role of the methylation cycle, folate intake and MTHFR activity may be a novel area of research as these are upstream for any specific epigenetic modifications seen in some of the reported biomarkers that may result in resistance to platinum-based drugs and/or other reported clinical outcome measures, in ovarian cancer patients. The upstream events associated with the hyper- and hypomethylation of key genes, associated with platinum resistance as presented in this review, are a novel area to be explored further with folate being a limiting factor in DNA, RNA and protein methylation.

This review accentuates the pleiotropic phenotypic complexities related to platinum therapy in ovarian cancer that a one-size-fits-all approach is both redundant and ineffective in a large portion of patients. This emphasises the need for a whole-system approach and personalised treatment strategies. Identifying key biomarkers to aid clinical decision-making is the first essential step in developing and appropriating therapies for at-risk patients, reducing toxicity and improving quality of life.

Author's contributions Caitlin Phillips Chavez (CPC), Dr. Michael Watson (MW), A/Prof Jermaine Coward (JC) and Dr. Janet Schloss (JS) contributed to the concept of the literature review. MW and JS oversaw the implementation of the literature review. CPC and MW conducted database screening. MW and JS checked the citations from full text. CPC completed the literature analysis. CPC wrote the first draft of the manuscript. MW, JC and JS conducted critical review of the draft manuscript with significant contributions to draft revisions and approval of the final manuscript for publication. CPC completed the final draft of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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