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Role of P53 and Ki-67 as Prognostic Factors in Ovarian Cancer: Systematic Review and Pooled-Analysis

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Abstract

Introduction: Ovarian Cancer (OC) is the most lethal cancer among gynecological malignancies. In the last years, several studies clarified that OC is characterized by different clinical entities that share only the anatomic site. The aim of this review is the evaluation of Ki-67 and p53 as prognostic factors in OC.

Methods: By searching Pubmed and abstracts from major cancer meetings, we selected clinical trials within the timeframe 2000-2016. We evaluated all data retrievable and we performed a pooled-analysis by random effect model. The endpoints were the Overall Survival (OS) in terms of Hazard Ratios (HRs) of survival outcomes.

Results: We observed a more severe outcome for patients over-expressing Ki-67. However, the overall data of our PFS meta-analysis did not reach the statistical significance (HR 1.98 CI 0.60-6.52, p=0.26). The indirect comparison of p53 studies, here reported, highlighted a possible correlation between patients OS and p53 status.

Conclusions: We hypothesize that both Ki-67 and p53 alterations retain a prognostic role in terms of OS in OC.

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Introduction

Ovarian Cancer (OC) is the most lethal gynecological malignancy. In the last years, several studies made clear that this neoplasm represents a "tree" of several entities that share only the anatomic site. Indeed, the molecular characteristics and recognized mutations show an unbalanced distribution among serous papillary, endometrioid or mucinous histologies [1]. More frequently p53 mutation, RAS pathway wild-type, BRCA mutations and Ki-67 over expression characterize a subgroup of OC (the high-grade serous tumour, high-grade endometrioid carcinoma, carcinosarcoma and undifferentiated tumors) according to "the Type II" described by Kurman et al. in a two-tier model of carcinogenesis. All these conditions seem to be promoted by de novo lesions with a genetic instability and present a strong correlation with response to platinum derivatives, probably due to early loss of BRCA and TP53 function [2,3]. Indeed, p53 is a central transcriptional mediator. By binding to DNA, p53 controls the expression of hundreds of target genes in order to control homeostasis and genome integrity. The Cancer Genome Atlas (TCGA) recently showed TP53 mutation in the 96% of 316 OC sequenced tumors [4]. Although the involved alterations include in-frame and frameshift insertions and deletions, missense and nonsense mutations, and splicing alterations, the most common oncogenic TP53 mutation is characterized by amino acid substitutions in the p53 protein [5,6]. Moreover, aneuploidy and somatic Copy Number Alterations (CNAs) are also frequently observed. Finally, some Missense Mutations (MMs) able to determine a gain-of-function p53 activity correlate with a benefit in survival outcomes in treated OC patients [7].

Ki-67 is a nuclear non-histone protein expressed during all active phases of the cell cycle. In different studies high levels of Ki-67 expression correlated with a poor prognosis [8,9]. Considering the high recurrence of p53 mutation and high expression of Ki-67 in OC, the aim of this review is to summarize the actual evidences and to clarify the possible prognostic impact of these factors in OC survival.

At present, the combination of carboplatin and paclitaxel could be considered the best treatment

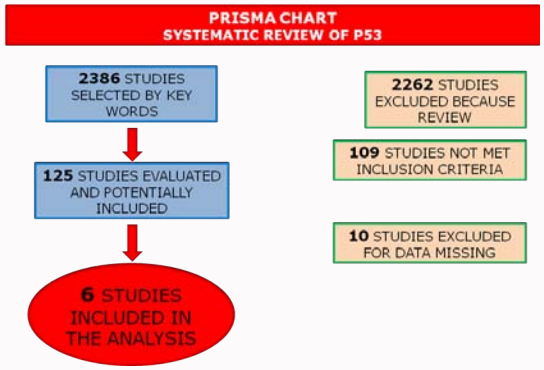

Figure 1: PRISMA chart related to published data in the timeframe 2000-2016. Only 6 studies were included in final analyses.

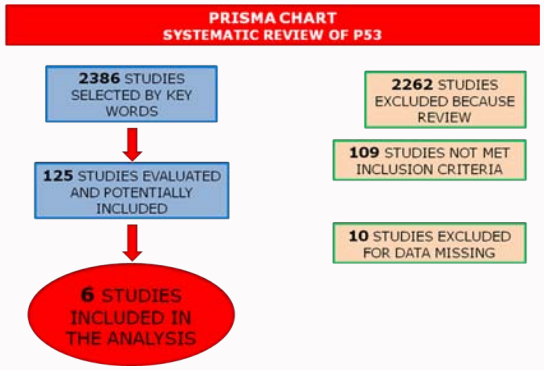

Figure 2: PRISMA chart related to published data in the timeframe (2000-2016). Only 5 studies were included in final analyses.

in ovarian cancer management [10]. However, many studies evaluated the prognostic and predictive role of p53 and BRCA mutations [7,11,12]. Specifically, BRCA mutations represent a biomarker predictive of sensitivity to PARP inhibitors treatment, approved by EMA for the use as single agent in the maintenance setting after a platinum- based treatment in BRCA1/2 mutation carrier patients [8,9,10]. Moreover, based on the systematic review and meta-analysis of the impact of Pegylated Liposomal Doxorubicin (PLD) compared to no-PLD-based regimens in ovarian cancer treatment, we observed no significant advantages in terms of OS, RR or Ca125-response [13].

Patients and Methods

Study design and data extraction

Systematic review of the Scientific Literature was performed by interrogating major dedicated search engines (PubMed). In order to select and collect homogeneous studies, two investigators (N.S. and E.I.) examined each trial, independently [14]. All discrepancies were resolved by an arbiter (P.T.). From selected trials, the following variables were analyzed and efficacy results were extracted: First author, number of patients enrolled, year of publication, treatment schedule, involved pathway, and so on. Efficacy endpoints here specified, including OS and Progression Free Survival (PFS) were analyzed. Data extraction was performed in accord to the PRISMA statement. The role of several genes (such as p53, Ki-67) was explored.

The selected keywords were: "ovarian", "ovary", "tumor", "cancer", "advanced", "metastatic", "therapy", "Ki-67", "p53" in different combinations. The 'related articles' function and references retrieved from articles were used to perform the search of all related studies, abstracts and citations. From selected trials identified, the following variables were evaluated and efficacy results were extracted: first author, number of patients enrolled, year of publication, treatment schedule, efficacy endpoints (OS, PFS, RR) if analyzed. Data extraction was in accord to the PRISMA guidelines.

Results

TP53

Study selection and characteristics: PRISMA chart related to published data is described in (Figure 1) considering a timeframe (2000-2016). The used key words were "epithelial""ovarian cancer", "p53" and "prognostic and/or predictive factor". Starting by 2386 articles identified using the pre-specified key words only 6 studies were included in final analyses [15,16]. All published phases II and III studies are reported in (Table 1). Moreover, 5 studies evaluated role of several p53 SNPs in term of OS. As previously reported and described, by the indirect comparison of p53 studies, it was possible to hypothesize a possible favourable correlation between patients OS and p53 status.

Ki-67

Study selection and characteristics: The PRISMA chart related to published studies is described in (Figure 2). We considered a timeframe (2000-2016). The used key words were epithelial ovarian cancer, Ki-67 and prognostic and/or predictive factor. Starting by 147 articles identified using the pre specified key words only 5 studies were included in final analyses [17,18].

We excluded reviews, comment and meta-analyses. All published phases II and III studies are reported in (Table 2).

OS and PFS analyses

For a total of 5 studies, 617 patients were enrolled in this meta-analysis. All patients presented an advantage stage (III-IV FIGO

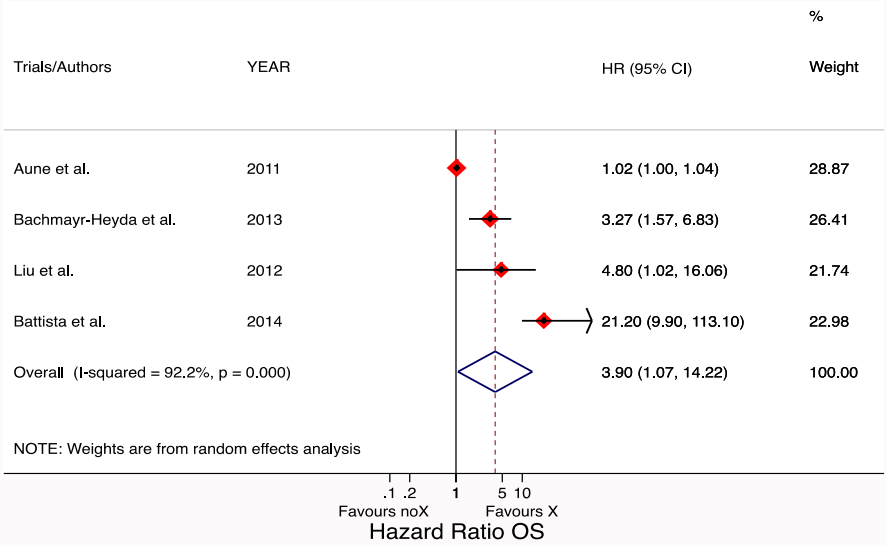

Figure 3: Comparison of OS according to involved studies. Abbreviation: overall survival, OS; hazard ratio, HR; progression free survival, PFS; over expression of Ki-67, X.

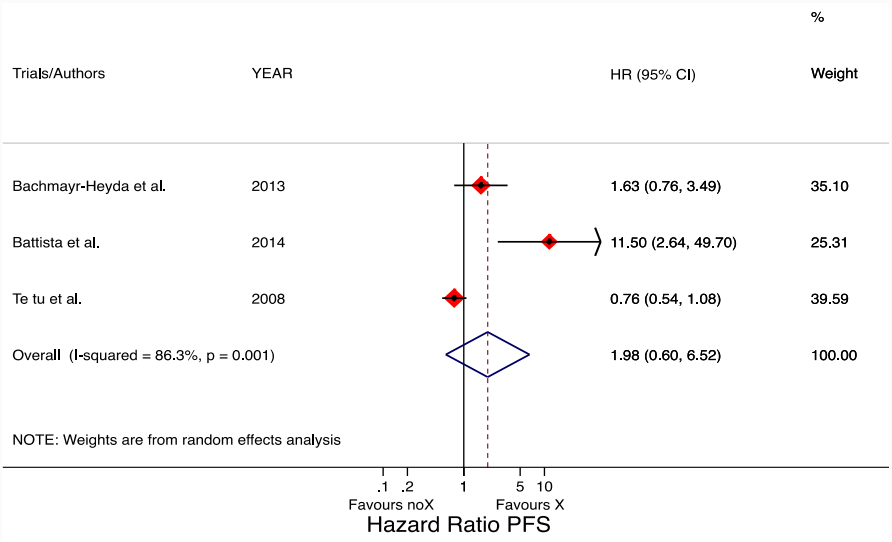

Figure 4: Comparison of PFS according to involved studies. Abbreviation: overall survival, OS; hazard ratio, HR; progression free survival, PFS; over expression of Ki-67, X.

stage). All patients received almost one line of platinum-based chemotherapy. In terms of OS, we showed that the over expression of Ki-67 (> 30%) indicated a poor prognosis (HR 3,91 Cl 1,07-14.19; p=0.03). Also concerning PFS analyses, we reported a more severe outcome for patients over-expressing Ki-67. In particular, the study of Battista et al. also showed in terms of PFS a HR of 11.5 [19]. However, the overall data of our PFS meta-analysis did not reach the statistical significance (HR 1.98 CI 0.60-6.52, p=0.26) (Figures 3,4).

Discussion

The systematic review of Literature on p53 status showed a potential prognostic role in terms of OS benefit in p53 mutated patients and a possible correlation with other genes such as Ki-67 as mitotic index. No conclusion on predictive role or for platinum-response can be demonstrated due to contradictory results of selected studies. As regard to Ki-67, our meta-analysis on 5 studies for a total of 617 patients confirmed a poor prognosis associated to high Ki-67 levels (HR 3.91). However, the studies characteristics did not allow a pooled analysis according to platinum-response. Moreover, in our mono-institutional analysis, we performed an exploratory study on p53 and Ki-67, in which despite the limited sample size, we were able to hypothesize a strong correlation between these factors and the OS In several studies, it was underlined that CA 125 level and Ki-67 expression could be associated with response to platinum salts, suggesting their predictive and prognostic role. In particular Ki-67>30% would seem to be predictive for complete response to platinum-based chemotherapy in advanced ovarian cancer (stages III-IV) [20,21].

At present, platinum-based regimens represent the gold standard of OC treatment. Response to platinum-based treatments represents the most important prognostic factor, because it is the only factor able to modify the OC patient outcome. Starting from this concept, the identification of platinum predictive biomarkers can be crucial in the clinical practice.

Table 1: Studies on p53 as prognostic factor in term of OS.

First Autor	Year	Study Design	FIGO stage	Patients Number	Histotype	Treatment (yes/no)	Performed analysis	Significance(p)	Follow up
Plisiecka-Halasa J[15]	2002	retrospective	II-IV	204	Mixed	CP/CAP	Correletion to p21 and p27 and cmyc	P=< 0.001	35.2
Sundov et al	2013	retrospective	I-IV	81	Serous		Correlation to MAPK,Kras, Topo2a, Braf, ki67	P=<0.003	
Tetu et al[17]	2008	retrospective	III-IV	158	Serous	CP	Microarrays on IHC of p53 and ki67 and correlation to selected genes	P=0.24	26
Rohlke P. et al.	1997	retrospective	I-IV	104	Serous	Platinum	P53 and correlation to clinical outcome	P=0.0028	Sep-96
Bartel et.al.	2008	retrospective	I-IV	107	Mixed	Platinum	P53 and correlation to clinical outcome	P=0.0016	
Zhang et.al[16]	2013	retrospective	I-IV	153	Nd	Neoadjuvant with platinum	P53 and correlation to clinical outcome	P=0.01	

Table 2: Studies on Ki67 as prognostic factor in term of OS.

First Autor	Year	Study Design	FIGO stage	Patients Number	Histotype	Treatment (yes/no)	OS (HR)	PFS (HR)	Follow up
Anue et al.	2011	retrospective	I-IV	90	mixed	CP/C	1.024	nd	
Bachmayar-Heyda et al.	2013	retrospective	I-IV	203	mixed	Platinum	3.27	1.63	
Tetu et al.[17]	2008	retrospective	III/IV	158	serous	CP	nd	0.76	26
Liu p et al.	2012	retrospective	I-IV	166	mixed	nd	4.8	nd	
Battista MJ et al.	2014	retrospective	I-IV	nd	mixed	nd	21.2	11.5	43.3

Concerning p53 and Ki-67, the potential prognostic role could represent, indirectly, a potential signal of different platinum-status. However, prospective studies are needed to this aim. In fact, the main limitation of this review is the small number of patients enrolled in each single study, the retrospective design, and the lack of aggregate analysis for p53. Our work needs to be considered in terms of "successful hypothesis" and the further proofs of validity can be expected in the near future. In the vision of personalized medicine, the availability of new biomarkers is a fundamental tool for the choice of treatment.

Contributions

NS, DC, EI performed the systematic review. NS and DC performed the meta-analysis of pooled data, PT, MTDM, PT, supervised the work. All Authors contributed to wrote and correct the paper.

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