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.
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, efficacy endpoints (OS, PFS, RR) if analyzed.

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: PRISMA chart related to
published data 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].

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
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 CI 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.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Study Design</th>
<th>FIGO stage</th>
<th>Patients Number</th>
<th>Histotype</th>
<th>Treatment</th>
<th>Performed analysis</th>
<th>Significance(p)</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plisiecka-Halasa J</td>
<td>2002</td>
<td>retrospective</td>
<td>II-IV</td>
<td>204</td>
<td>Mixed</td>
<td>CP/CAP</td>
<td>Correlation to p21 and p27 and onyc</td>
<td>P=&lt;=0.001</td>
<td>35.2</td>
</tr>
<tr>
<td>Sundov et al</td>
<td>2013</td>
<td>retrospective</td>
<td>I-IV</td>
<td>81</td>
<td>Serous</td>
<td>CP</td>
<td>Correlation to MAPK, Kras, Topo2a, Braf, k67</td>
<td>P=&lt;=0.003</td>
<td></td>
</tr>
<tr>
<td>Tetu et al[17]</td>
<td>2008</td>
<td>retrospective</td>
<td>III-IV</td>
<td>158</td>
<td>Serous</td>
<td>CP</td>
<td>Microarrays on IHC of p53 and k87 and correlation to selected genes</td>
<td>P=0.24</td>
<td>26</td>
</tr>
<tr>
<td>Rohlike P. et al.</td>
<td>1997</td>
<td>retrospective</td>
<td>I-IV</td>
<td>104</td>
<td>Serous</td>
<td>Platinum</td>
<td>P53 and correlation to clinical outcome</td>
<td>P=0.0028</td>
<td>Sep-96</td>
</tr>
<tr>
<td>Bartel et al.</td>
<td>2008</td>
<td>retrospective</td>
<td>I-IV</td>
<td>107</td>
<td>Mixed</td>
<td>Platinum</td>
<td>P53 and correlation to clinical outcome</td>
<td>P=0.0016</td>
<td></td>
</tr>
<tr>
<td>Zhang et al[16]</td>
<td>2013</td>
<td>retrospective</td>
<td>I-IV</td>
<td>153</td>
<td>Nd</td>
<td>Neoadjuvant with platinum</td>
<td>P=0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Study Design</th>
<th>FIGO stage</th>
<th>Patients Number</th>
<th>Histotype</th>
<th>Treatment</th>
<th>OS (HR)</th>
<th>PFS (HR)</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anue et al.</td>
<td>2011</td>
<td>retrospective</td>
<td>I-IV</td>
<td>90</td>
<td>mixed</td>
<td>CP/C</td>
<td>1.024</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>Bachmayar-Heyda et al.</td>
<td>2013</td>
<td>retrospective</td>
<td>I-IV</td>
<td>203</td>
<td>mixed</td>
<td>Platinum</td>
<td>3.27</td>
<td>1.63</td>
<td></td>
</tr>
<tr>
<td>Tetu et al.[17]</td>
<td>2008</td>
<td>retrospective</td>
<td>III-IV</td>
<td>158</td>
<td>serous</td>
<td>CP</td>
<td>nd</td>
<td>0.76</td>
<td>26</td>
</tr>
<tr>
<td>Liu p et al.</td>
<td>2012</td>
<td>retrospective</td>
<td>I-IV</td>
<td>166</td>
<td>mixed</td>
<td>nd</td>
<td>4.8</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>Battista MJ et al.</td>
<td>2014</td>
<td>retrospective</td>
<td>I-IV</td>
<td>nd</td>
<td>mixed</td>
<td>nd</td>
<td>21.2</td>
<td>11.5</td>
<td>43.3</td>
</tr>
</tbody>
</table>

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 aim this. 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, MTD, PT, supervised the work. All Authors contributed to wrote and correct the paper.

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References


