Correlations between P53 mutations and response to Paclitaxel/Cisplatin Chemotherapy in Patients with Advanced Epithelial Ovarian Cancer

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Abstract: Background and Objective: The p53 gene plays an important role in cellular response to DNA damage and has been implicated in the response to platinum compounds in patients with ovarian carcinoma. Because taxanes could induce p53-independent apoptosis, we studied the relevance of p53 gene status to response in ovarian carcinoma patients receiving paclitaxel and platinum-containing chemotherapy. **Patients And Methods:** Thirty-three previously untreated patients with advanced disease received standard paclitaxel/platinum-based chemotherapy. In tumor specimens collected at the time of initial surgery, before therapy, p53 gene status and expression were examined by single-strand conformation polymorphism (SSCP) sequence analysis. **Results:** Twenty three (70%) of the 33 patients had a clinical response. *p53* mutations were detected in 20 (60%) of 33 tumors. Among the patients with mutant *p53* tumors, 17 patients (85%) responded to chemotherapy. Six (46%) of 13 patients with wild-type *p53* tumors responded to the same treatment. The overall response rate and the complete remission rate were significantly higher among patients with mutant *p53* tumors than among patients with wild-type *p53* tumors (P = 0.008). **Conclusion:** Treatment with paclitaxel in combination with standard platinum doses is more effective in patients with mutant *p53* ovarian tumors. Determining *p53* mutational status can be useful in predicting therapeutic response to drugs effective in ovarian carcinoma.
[Alaa Fayed, Sherin A. Shazly and Amal F. Gharib. **Correlations between P53 mutations and response to Paclitaxel/Cisplatin Chemotherapy in Patients with Advanced Epithelial Ovarian Cancer.** *J Am Sci* 2015;11(5):232-238]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 27. doi:10.7537/marsjas110515.27

Key words: P53, Ovarian Carcinoma, chemotherapy.

1.Introduction

Worldwide, ovarian cancer has been estimated to affect 225 500 women and claim 140 200 lives annually [1]. The majority of ovarian cancers are of epithelial origin and consist of four major morphological subtypes: serous, endometrioid, clear cell and mucinous. Low-grade serous and mucinous carcinomas may develop in stepwise fashion from adenomas to carcinomas, while clear cell and endometrioid carcinomas often arise from endometriosis. In contrast, highgrade serous (HGS) carcinomas develop from an undefined precursor lesion and may progress rapidly without obvious intermediate steps. Due to this rapid progression, as well as the lack of specific symptoms and effective early detection methods, HGS ovarian carcinomas are the most lethal subtype, being primarily diagnosed at advanced stages. Consequently, early stage HGS ovarian carcinoma is rare [2].

Ovarian carcinoma is recognized as a one of the most chemo-responsive solid tumors. A large number of cytotoxic agents, including platinum compounds, antimicrotubule agents, alkylating agents, and topoisomerase inhibitors, have been used in the treatment of advanced ovarian carcinoma. Combination of platinum-paclitaxel chemotherapy has become a standard treatment for advanced-stage disease. [3]

Many trials have proved that the Outcome with this treatment is markedly improved in comparison with other platinum-containing regimens. However, the cellular basis of the efficiency of platinum-paclitaxel combinations needs to be defined. In particular, the development of cisplatin-resistant cell populations can be decreased by the capability of taxanes to overcome cisplatin resistance. A good understanding of the molecular or biologic outline of human carcinoma cells, exquisitely responsive to the different classes of agents, can lead to the proper plan of treatment regimens that are more efficient in different subgroups of patients. [4]

The induction of apoptosis was identified by many trials to be the most important mode of drug-induced cytotoxicity in sensitive cells [5,6]. The wild type P53 gene product is proved to be involved in cellular response to some of the cytotoxic insult by repair of DNA, modulation of cell cycle regulation and triggering of signals that leads to apoptosis [7]. Thus resistance to cisplatin and other DNA damaging drugs can be caused by inactivation of the P53 gene as a result of decreased cell susceptibility to start the apoptotic response. Consistent with this theory is the observation that missense mutations are combined

with cisplatin resistance in a clinical setting [8]. However, in contrast, in a preliminary study, patients having tumors with mutated p53 genes were found to have better response to paclitaxol based therapy [9].

This finding is consistent with the unique mechanism of action of taxanes (i.e., alterations of microtubule function), because the presence of a functional p53 gene is not required for induction of apoptotic cell death by anti-microtubule agents. Cellular pharmacology studies support the concept of an increased sensitivity of mutant p53 cells to taxanes, as a consequence of an accumulation of treated cells in the G2-M phase.[10] The efficacy of taxanes against mutant p53 ovarian carcinoma may also have relevant clinical implications, in light of the evidence that p53 mutation is a poor prognostic marker for this tumor.[11] To study the role of *p53* status in clinical response to chemotherapy and its prognostic significance in ovarian carcinoma, we conducted the present study.

2. Patients And Methods

Patients and treatment protocol

The study population consisted of 33 untreated patients with International Federation of Gynecology and Obstetrics [12] stage III and IV epithelial ovarian cancer enrolled between 2008 and 2013. All patients were subjected to standard operative procedures; in all cases an attempt was made to optimally debulk the grossly recognizable tumor, and the amount of residual disease at completion of debulking surgery was recorded as none, less than or equal to 2 cm, and more than 2 cm. Within 2 to 3 weeks of surgery, all patients were treated with induction chemotherapy consisted of cisplatin 75 mg/m^2 and paclitaxel 135 mg/m^2. The median number of cycles of induction chemotherapy administered was 6 (range 2 to 9). Gynecologic examinations, abdominal or pelvic ultrasonography, CA-125 assays, and radiologic investigations were performed monthly as needed, to assess clinical response, which was rated using World Health Organization (WHO) criteria. Clinically complete responders underwent second-look laparoscopy. In laparoscopy-negative patients, second-look laparotomy was performed to assess the pathologic response, using conventional surgical and pathologic procedures. The patients who achieved a pathologic CR or a PR were considered responsive to therapy. The sites of persistence and the volume of residual disease after induction chemotherapy were carefully histologically assessed.

Patients who initially had only an exploratory laparotomy underwent a second laparotomy after chemotherapy for cytoreduction. Further management depended on the results of these procedures. In general, patients responding to chemotherapy received three to four additional cycles of chemotherapy. Those with non-responsive disease were treated with salvage second-line chemotherapy. Every three months a complete physical and gynecological examination of the patients was performed. A CT scan was done every six months during the first two years or more often if clinically indicated.

Molecular Analysis of *p53*

We screened all tissue samples by nested polymerase chain reaction (PCR)-single-strand conformational polymorphism (SSCP) analysis to discover the presence of p53 gene mutations in the most commonly affected exons (5 to 9) of the gene.[13,14] We prepared DNA from frozen specimens by Pronase digestion and phenol extractions following the standard procedures. SSCP analysis for the detection of p53 gene mutation was described previously. [15]

PCR amplified exons showing abnormal migrations as well as randomly chosen PCR-amplified exons showing normal migrations were subjected to direct DNA sequencing with AmpliCycle Sequencing kit (Perkin-ElmerCetus, Branchburg, NJ). Each sequencing reaction was performed at least twice, analyzing separate amplifications. In each case, the detected mutation was confirmed in the sequence as sense and antisense strands.

Statistical Analysis

Data were entered, checked and analyzed using the SPSS Software system (version 11.0; Chicago, IL).

3. Results

Response to chemotherapy

Among the 33 patients who enrolled into the study, 15 (46%) achieved complete responses, 8 (24%) achieved partial remission, and 10 (30%) had minimal or no response. (Table 1)

Table 1. Clinicopathologic Characteristics of Patients

Characteristic	No. of Patients (N = 33)
Age	
≤60 years	25
> 60 years	8
Histologic type	
Serous	28
Endometrioid	4
Undifferentiated	1
Grade of differentiation	
GI-GII	6
GIII	27
FIGO stage	
III	26
IV	7
Residual tumor	
< 2 cm	13
2-5 cm	12
Unresectable (multiple biopsies)	8
Clinical response to chemotherapy	
Objective response	23
No response	10

Frequency and Spectrum of *p53* Mutations

Nested PCR-SSCP was performed successfully in all 33 cases. Exons 5 to 9 of the p53 gene were examined for mutations. PCR-amplified exons, showing abnormal migrations and suspected for mutations, were further analyzed by direct DNA sequencing. Overall, among the 33 tumors examined, 20 mutations (60%) were found. Details of the identified genetic changes are presented in Table 2. Five mutations were located in exon 5, four in exon 6, six in exon 7, and five in exon 8.

Table 2. Clinicopathologic features of 33 Ovarian Carcinoma Patients and p53 Status

Patient No.	FIGO Stage	Grade	Histologic Type	p53 Status	Response
1	IIIC	G1	Serous	Exon 5/codon 172 GTT > TTT/Val > Phe	CR
2	IIIC	G2	Serous	Exon 6/codon 216 GTG > ATG/Val > Met	CR
3	IIIC	G3	Serous	Exon 5/codon 175 CGC > CAC/Arg > His	CR
4	IIIB	G3	Serous	Exon 7/codon 241 TCC > TAC/Ser > Tyr	CR
5	IV	G3	Serous	Exon 8/codon 271 GAG > TAG/Gln > stop	CR
6	IIIC	G3	Endometrioid	Exon 5/codon 151 CCC > CAC/Pro > His	CR
7	IIIA	G3	Serous	Exon 6/codon 220 TAT > TGT/Tyr > Cys	CR
8	IIIB	G3	Serous	Exon 7/codon 248 CGG > TGG/Arg > Trp	CR
9	IV	G3	Serous	Exon 7/codon 248 CGG > TGG/Arg > Trp	CR
10	IV	G3	Serous	Exon 8/codon 271 GAG > TAG/Gln > stop	CR
11	IIIB	G3	Serous	Wild-type	CR
12	IIIC	G3	Serous	Exon 5/codon 179 CAT > CGT/His > Arg	PR
13	IV	G2	Undifferentiated	Exon 8/codon 273 CGT > CTT/Arg > Leu*	PD
14	IIIC	G1	Endometrioid	Exon 8/codon 272 GTG > TTG/Val > Leu	PR
15	IIIC	G3	Serous	Exon 6/codon 216 GTG > ATG/Val > Met	PR
16	IIIC	G3	Serous	Exon 6/codon 194 CTT > CCT/Leu > Pro	PR
17	IIIC	G3	Serous	Exon 7/codon 234 TAC > TGC/Tyr > Cys	PD
18	IV	G3	Serous	Wild-type	PR
19	IIIB	G3	Serous	Wild-type	CR
20	IIIB	G3	Serous	Wild-type	CR
21	IIIB	G3	Endometrioid	Wild-type	PD
22	IV	G3	Serous	Exon 7/codon 248 CGG > TGG/Arg > Trp	PR
23	IIIC	G3	Serous	Wild-type	PD
24	III	G3	Serous	Wild-type	CR
25	IIIC	G2	Serous	Wild-type	PR
26	IIIC	G3	Serous	Exon 5/codon 181 CGC > CCC/Arg > Pro	SD
27	IIIC	G3	Serous	Wild-type*	SD
28	IV	G2	Serous	Wild-type	SD
29	IIIC	G3	Serous	Exon 7/codon 239 1bp deletion/stop	PR
30	IIIB	G3	Endometrioid	Exon 8/codon 282 CGG > TGG/Arg > Trp	CR
31	IIIB	G3	Serous	Wild-type	PD
32	IIIC	G3	Serous	Wild-type	SD
33	IIIC	G3	Serous	Wild-type	PD

Relationship between Response to Therapy and Molecular, Clinical, and Pathologic Features

We divided the response of tumor into two categories to determine if there is an association between the response of chemotherapy and the status of P53 gene or pathological or clinical features. These two categories were no response and response, which included partial or complete response. The size of the residual tumor appeared to be highly correlated with the response to therapy; the response rate was lower in patients with large (>2 cm.) residual disease than in patients having less than 2 cm residual disease (75% vs. 85%). It was apparent that patients with low grade tumor (G I, II) had lower response rate than other patients with less differentiated tumors (P=0.032). However, the most relevant observation of this study was a statistically significant association between the mutational status of p53 and response to therapy (P = 0.008). Seventeen (85%) of 20 patients with mutant p53 responded, whereas six (46%) of 13 patients with wild-type p53 achieved an objective response. The association between p53 molecular status and

response was maintained in multivariate analysis (P = .024) after controlling for grade of differentiation and residual tumor (Table 4).

Table 3. Univariate Analysis of Clinicopathological Parameters and p53 Status according to Clinical Response to Chemotherapy

Characteristic	No. of Patients	Clinical Response				P^*
		Response		No response		
		No.	%	No.	%	
Total	33	23	70	10	30	
Age						
≤60 years	25	16	64	9	36	0.13
> 60 years	8	7	88	1	12	
Histologic type						
Serous	28	22	79	6	21	0.098
Endometrioid	4	3	75	1	25	
Undifferentiated	1	0	00	1	100	
Grade of differentiation						
I-II	6	2	33	4	67	0.032
III	27	21	78	6	22	
FIGO stage						
III	26	20	77	6	23	0.12
IV	7	4	57	3	43	
Residual tumor						
< 2 cm	13	11	85	2	15	0.091**
2-5 cm	12	9	75	3	25	
Unresectable (multiple biopsies)	8	4	50	4	50	
***p53* molecular status**						
Wild-type	13	6	46	7	54	0.008
Mutant	20	17	85	3	15	

*Fisher's exact test for proportion.

**Percentage of response among patients with residual tumor measuring < 2 cm versus that among patients with tumors measuring 2-5 cm or unresectable tumors.

Table 4. Multivariate Analysis of Clinicopathologic Parameters and p53 Mutational Status according to Clinical Response to Chemotherapy

Characteristic	$\times^2$	P
p53 molecular status	5.25	0.026
Residual tumor	4.51	0.038
Grade of differentiation	2.02	0.13

With a median follow-up of 29 months, fifteen deaths were recorded: ten among the patients with mutant *p53* tumors and five among patients with wild-type *p53* tumors. As a consequence, the actuarial survival analysis did not show a significant difference between the subgroups. However, patients with mutant *p53* had an appreciably increased progression-free survival time (median progression-free survival time, 19 months among patients with mutant *p53* tumors and 9 months among patients with wild-type *p53* tumors; P = 0.09). Relevant to this point is the observation that patients with wild-type *p53* tumors who did not achieve complete remission with first-line therapy were in most cases still responsive to a second-line therapy. Thus, it is conceivable that second-line therapy influenced survival in this group of patients.

4. Discussion

Alterations of the p53 gene have been implicated in tumor aggressiveness, since mutations of p53 was reported to be associated with shorter disease-free survival and poor clinical outcome of ovarian cancer patients.[16,17]

Several publications supports the concept that specific alterations of tumor cells, involving the expression of certain oncogenes or inactivation of tumor suppressor genes, may have a critical effect on cellular response to cytotoxic injury.[18,19,5] Because alterations may involve cell death pathways, it is conceivable that they might play an important role in determining resistance. Mutations of the p53 tumor suppressor gene represent the most frequent molecular alterations in ovarian carcinoma; such mutations are found in more than 50% of patients with advanced

disease.[20] p53 functions involve to DNA repair, cell cycle control, stress response, genomic stability, cell senescence, and apoptosis.[18,19] Thus, failure of p53 function could play a role in tumor progression. Relevant to this point is the observation that advanced-stage disease is more commonly coupled with drug resistance.[8] Consistent with the involvement of wild-type p53 function in response to DNA-damaging agents is the observation that mutations of p53 were associated with lack of response to cisplatin therapy in ovarian carcinoma patients.[9] If p53 deactivation is the most relevant factor to determine drug resistance, it is possible that mutant p53 tumors maintai sensitivity to agents able to activate a p53-independent apoptosis. Among such agents, the taxanes are now acknowledged as the best drugs to be used in combination with platinum compounds.[21]

In our study there was a group of advanced ovarian cancer patients that had clinicopathologic features comparable with those in the other studies [22]. In our study the efficiency of the standard paclitaxel-platinum combination regimen, in term of objective response (70%), matched with the clinical results of other studies that used the same regimen [22]. Our study supplied us with proofs that paclitaxel based combinations that included standard doses of platinum are efficient to treat tumors with mutant P53. The overall response rate was significantly higher among patients with mutant p53 tumors than among patients with wild-type p53 tumors. This result is consistent with preclinical evidence of increased sensitivity of ovarian carcinoma cells after deactivation of p53 [23,24]. The molecular basis for sensitization of ovarian carcinoma cells to anti-microtubule drugs after inactivation of p53 is still unknown. Alterations in expression of microtubule-stabilizing proteins or mitotic checkpoint proteins and/or changes in cell cycle progression as a result of loss of p53 function could play a role in starting a p53-independent pathway of apoptosis. [10,24] Such a pathway still includes the Bcl-2 protein. Inactivation of p53 causes over expression of Bcl-2, which is under the negative control of p53.[25] Since elevated levels of Bcl-2 may be a resistance mechanism for genotoxic antitumor agents through suppression of apoptosis. [26] The ability of paclitaxel to induce phosphorylation of Bcl-2 can explain the effectiveness (and likely the synergistic interaction) of paclitaxel and its combination with platinum containing chemotherapy in mutant p53 tumors. [24] In the our study, molecular analysis of p53 gene mutations was limited to the most frequently affected exons [22]. In our study, we found that the frequency of P53 mutation (60%) in our advanced ovarian cancer patients was comparable to other frequencies in other studies [6,27].

In our study there was a relatively low response rate in patients who had wild-type p53 tumors. Of the 13 patients with wild-type p53 tumors, only two had partial remission and four (31%) had a complete remission, for an overall 46% response rate. An explanation for the moderate efficiency of the chemotherapy containing platinum and paclitaxel, in contrast to the marked efficiency of high-dose cisplatin therapy, in patients with wild-type p53 tumors could be that the dose of the DNA-damaging agent was inadequate to trigger an efficient p53-dependent apoptosis. [28,29] If this hypothesis is correct, full doses of DNA-damaging agents (platinum and alkylating agents) should be preferred in first-line therapy for ovarian carcinoma with wild-type p53. The results also imply that the efficiency of adding taxanes and platinum compounds can be credited to the exquisite efficiency of the combination against mutant p53 tumors and that the use of paclitaxel in the treatment of wild-type p53 tumors may be doubtful.

A number of other clinicopathologic and biologic factors may have influenced the pattern of response. In particular, a significant association was found in our study between response and degree of differentiation (P = 0.032) or residual tumor (P = 0.091). Cases of resistant wild-type p53 tumors included seven cases. Given these considerations and the limitations of the design of the present study, p53 status cannot be regarded as the sole determinant of response. For example, it is likely that other factors are responsible for the level of resistance in patients with tumors carrying wild-type p53, because, as observed in previous study,[9] no precise correlation was found in this subset of patients between complete remission and presence of wild-type p53.

The present results may have relevant pharmacologic implication, in which, patients with mutant p53 tumors, which are expected to be relatively resistant to platinum compounds,[9] seem to be responsive to paclitaxel in combination with platinum compounds. Because the therapeutic success of the combination seems to reflect the effectiveness of the agents on different cellular populations carrying different genetic backgrounds rather than the result of a synergistic interaction, p53 status assessment could be helpful in selecting subgroups of patients who would advantage from a tailored treatment. If this hypothesis is confirmed, it is conceivable that the optimal therapeutic potential of taxanes and platinum compounds could be achieved with sequential or alternating regimens that allow the use of full doses of the most effective agents.

In conclusion, the our results provided a rational basis on how to understand the heterogeneity of tumor response to efficient drugs with a variable mode of action and for the development of more efficient drug

plans based on the molecular profiles of relevant apoptosis-related characteristics.

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5/21/2015