p-53 gene mutations as a predictive marker in a population of advanced breast cancer patients randomly treated with doxorubicin or docetaxel in the context of a phase III clinical trial

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Background: Preclinical data indicate that p-53 gene mutations predict resistance to doxorubicin (A) but not to docetaxel (Taxotere) (T). In the TAX 303 trial, A and T have been compared with advanced breast cancer patients.

Patients and methods: Primary tumor samples from patients participating in the TAX 303 trial were collected. p-53 gene mutations were evaluated by denaturing high-performance liquid chromatography (DHPLC) and confirmed by sequencing. Topoisomerase II alpha (topo II α) protein levels were evaluated by immunohistochemistry. Clinical and biological data were correlated.

Results: Tumor samples for DHPLC analysis were available for 108 of 326 patients from the clinical trial. p-53 gene mutations were observed in 20% of patients. In patients with a mutated p-53 gene, a trend for a lower percentage of responders was observed in the A arm (17%) compared with the T arm (50%). In the wild-type p-53 cohort, response rates to A and T were 27% and 36%, respectively.

Of the 16 patients carrying wild-type p-53- and topo II protein-positive tumors, seven (44%) responded to anthracyclines, while response rate to the same drug was 13% in the remaining cohorts [odds ratio 5.06 (95% confidence interval 1.19–21.41), P = 0.03]. The combination of the two markers had no predictive value in patients treated with docetaxel.

Conclusions: (i) p-53 gene analysis indicates that gene mutations may compromise the efficacy of A while they do not interfere with the antitumor activity of T; and (ii) the evaluation of multiple molecular markers including p-53 and proliferation markers as topo II protein levels looks more promising in predicting response to anthracyclines.

Key words: cytotoxics, molecular markers, topoisomerase II alpha

introduction

It is now clear that breast cancer biology heterogeneity is responsible for individual responses to the same treatment. In the last decade several efforts have been made in an attempt to identify molecular predictors of response to anticancer agents. This achievement would allow for a more targeted and tumor biology-driven approach to breast cancer medical treatment.

Almost 10 years ago, O’Connor et al. [1] reported in vitro data indicating that cell lines from the National Cancer Institute Anticancer Drug Screening Panel, carrying mutant sequences of the p-53 gene, tended to exhibit less growth inhibition than the wild-type cell lines when treated with DNA-damaging agents such as alkylating compounds and anthracyclines.

Conversely, growth inhibitory activity of anti-microtubule agents, such as taxanes, tended to be independent of the p-53 gene status [1]. The results of this preclinical study were challenged later on by some methodological caveats such as the use in the O’Connor study of a short-term assay, which cannot detect growth inhibition effects of
DNA-damaging agents, usually delayed in p-53 mutated cell lines [2]. At the same time, these preclinical data prompted the activation of a series of retrospective clinical studies testing the concept that taxanes might be more effective than anthracyclines in patients carrying p-53 gene-mutated tumors [3, 4].

In 1999, Chan et al. [5] reported the results of a phase III clinical trial (TAX 303) comparing doxorubicin with docetaxel as first/second-line treatment of advanced breast cancer patients. Because of its unique design (i.e. both cytotoxics delivered at full doses as single agents), the TAX 303 clinical trial represented a unique opportunity to identify molecular markers predicting for either sensitivity or resistance to both agents. Supported by this background, in January 2000 we started the collection of paraffin-embedded primary tumor samples from patients participating in the TAX 303 trial. A panel of biological markers potentially involved in the prediction of response to doxorubicin and/or docetaxel was investigated. The results of the interaction between HER-2 gene status, topoisomerase II alpha (topo II α) protein levels, and treatment efficacy have already been reported [6, 7]. Here, we report the results of the interaction between p-53 gene mutations and response to docetaxel and doxorubicin.

Moreover, supported by the results of the two previously reported studies [6, 7], in the present article we attempt to correlate response to these cytotoxics with breast cancer subtypes defined through p-53 and topo II α status.

**Patients and methods**

**Clinical trial**

An extensive description of patients and methods of the TAX 303 trial has already been published [5]. In brief, advanced breast cancer patients were randomly treated with doxorubicin 75 mg/m² or docetaxel (Taxotere; Sanofi-Aventis, Paris, France) 100 mg/m², both agents delivered on day 1 every 21 days. All patients had to have received previous treatment with CMF (cyclophosphamide, methotrexate, and fluorouracil), either in the adjuvant or in the metastatic setting. No more than one line of treatment of advanced disease was allowed, and no previous treatment with anthracyclines, antracyclines, or taxanes was allowed.

The trial was a randomized, nonblinded prospective phase III study. Treatment was continued for a maximum of seven cycles in the absence of disease progression and/or unacceptable toxicity. A complete tumor assessment was carried out before registration in the study, during treatment (i.e. after cycles 2, 4, and 7, or upon discontinuation of study treatment), and at least every 3 months until disease progression during the follow-up period. Objective responses were evaluated according to the World Health Organization criteria [8]. The sample size of the study was calculated with the primary aim to detect a 50% increase in median time to progression (TTP) with a 5% two-sided type I error and 90% power.

**Translational research study**

**Tumor samples collection.** The translational research study was first approved by the ethics committee of the Jules Bordet Institute (JIB) in Brussels, which served as the coordinating center for this retrospective study. Afterwards, the list of patients entered in the clinical trial was submitted to each participating center, which had to provide the coordinating center with one paraffin-embedded sample representative of the primary tumor for each patient entered in the clinical trial. Samples were sent by the participating centers to the coordinating center by conventional mail. Once samples were received, they were classified and stored at room temperature until the predictive marker analysis was carried out.

**DNA extraction and PCR.** All procedures related to p-53 gene evaluation were carried out at the Institute of Medical Technology, University of Tampere, Finland. At the time of p-53 gene testing, researchers from this laboratory were blinded with regard to treatment assignment and clinical outcome.

Genomic DNA was extracted and purified from paraffin-embedded tumor specimens using a QIAamp Mini Kit using the manufacturer’s recommended protocol for paraffin-embedded tissue samples (QIAGEN, Hilden, Germany). Fifty nanograms of the genomic DNA was amplified in a PCR reaction containing 0.6 × Platinum PCR Buffer (Invitrogen, Carlsbad, CA), 1.4–2.4 mM MgCl2, 160 μM dNTPs (Clontech, Palo Alto, CA), 0.3 μM forward and reverse primers, DNA polymerases AmpliTaq Gold (1.25 units; Applied Biosystems, Branchburg, NJ), and Platinum Taq (1.25 units; Invitrogen) in a volume of 50 μl. The forward and reverse oligonucleotide primers used to amplify p53 exons 5–9 are listed in Table 1. The PCR cycling conditions consisted of an initial denaturation step at 94°C for 14 min, following 35 cycles at 94°C for 30 s, annealing at 55–58°C for 30 s and 1 min at 72°C, and final extension for 10 min at 72°C. Heteroduplex formation was created by denaturing the PCR products for 5 min at 95°C, and then allowing the samples to reanneal by decreasing the temperature 1°C per min from 95°C to 40°C.

**P-53 gene mutations by denaturing high-performance liquid chromatography.** Denaturing high-performance liquid chromatography (DHPLC) analysis was done using Agilent Technologies’ series 1100 HPLC system (Agilent Technologies, Palo Alto, CA). Five to 10 μl of the PCR product was injected on the Helix DNA HPLC Column 50 × 0.5 mm (Varian Inc., Walnut Creek, CA), and eluted at a flow rate of 0.45 ml/min within a linear acetonitrile gradient consisting of a mixture of buffer A (100 mM triethylammonium acetate and 0.1 mM EDTA; Varian Inc.), and buffer B (100 mM triethylammonium acetate, 0.1 mM EDTA and 25% acetonitrile; Varian Inc.). The DYS271 standard, which consists of a 209-base-pair (bp) fragment of double-stranded DNA and heterozygous with an A to G mismatch at position 168, was used to control column resolution. In addition, a positive mutation control for each of the tested exons was used as follows: PC-3 cell line for exon 5 (deletion 1 bp, codon 138), DU-145 cell line for exon 6 (G > T, codon 223), BT-549 cell line for exon 7 (G > C, codon 249), BT-474 cell line for exon 8 (G > A, codon 249), and BT-549 cell line for exon 9 (intron single-nucleotide polymorphisms T > G, +12 bp). To establish the separation conditions, DHPLC analysis was carried out after mixing the cell lines with wild-type DNA (lymphocyte DNA) at a ratio of 2 : 1. The elution temperatures for each amplicon were obtained from the DHPLC Melt Program (http://insertion.stanford.edu/melt.html), and then optimized by studying alterations in the elution profiles of the samples within a temperature range of ±3°C under and above the indicated melting temperature. The temperature that best separated homoduplexes was used for DHPLC analysis. The annealing temperatures for different p53 exons and the elution temperatures used during DHPLC are given in Table 1.

**DNA sequencing.** Samples with an abnormal elution profile in DHPLC as compared with a control consisting of lymphocyte DNA were subjected to automate sequencing. The PCR products were first purified using a Montage DNA purification column (Millipore Corp., Bedford, MA). Direct sequencing of PCR products was carried out using BigDye3 termination chemistry (Applied Biosystems) and an ABI 3100 Genetic Analyzer (Applied Biosystems) according to the instructions provided by the manufacturer.

**Topo II α protein evaluation.** Topo II α protein status was evaluated by immunohistochemistry at the JIB—Brussels, as previously reported [9]. Briefly,
sections were pretreated with trypsine. The primary antibody was clone KiS1 by Boerhinger-Manheim, Germany. Topo IIα staining was treated as a continuous variable (% of immunostained cells). Moreover, an arbitrary cut-off for definition of topo IIα-positive and -negative samples was established (i.e. topo IIα-positive samples: >10% of immunostained cells) based on a previous experience indicating that 10% was the median percentage of immunostained cells in a population of almost 400 breast cancer patients [9].

When topo IIα evaluation was carried out, pathologists were blinded with regard to treatment assignment and clinical outcome.

**statistical analysis.** Response rate was defined as the percentage of patients in each treatment group that achieved a complete or partial response. The patients evaluated in the present study were a subgroup of the study population entered into the prospective clinical trial. To evaluate the representativeness of this subgroup, main patient characteristics, as well as study treatment activity, were compared between the cohort of patients with available tumor samples who participated in the present study and the cohort of patients without available samples who did not. To this end, the Mann–Whitney statistical test was used for age (continuous variable), and chi-square test for all the other variables (categorical variables).

The probability of achieving an objective response was estimated by fitting the data with univariate logistic regression models. The following covariates were examined: p53 gene status (wild type, mutated), topo IIα protein status (positive, negative), Karnofsky performance status (PS) (60–70, >80), visceral involvement (yes, no), and number of metastatic sites (≤2, >2). Their significance was tested using likelihood ratio tests with a significance level of 0.05. Odds ratios (ORs) were calculated with 95% confidence intervals (CIs).

To test the hypothesis that treatment activity could interact with the evaluated covariates, an interaction term combining the treatment arm and each investigated covariate was added to the logistic regression model.

**results**

**clinical trial**

The clinical trial results have been reported extensively [5]. In brief, in the 326 advanced breast cancer patients participating in the study, the overall response rate was significantly higher with docetaxel (T) than with doxorubicin (A) (47.8% versus 33.3%, respectively; P = 0.008). Median TtP was slightly longer in the docetaxel than in the doxorubicin group (26 versus 21 weeks, respectively, P = 0.45), while median survival was similar in the two treatment groups (docetaxel 15 months, doxorubicin 14 months).

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**Table 1.** The oligonucleotide primers and the annealing and elution temperatures used

<table>
<thead>
<tr>
<th>Primers (5′→3′)</th>
<th>Forward</th>
<th>Reverse</th>
<th>Fragment size (bp)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Annealing</td>
</tr>
<tr>
<td>p53 5</td>
<td>CAC TTG TGC CCT GAC TTT CA</td>
<td>ACC AGC CCT GTC GTC TCT C</td>
<td>266</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>AGA GAC GAC AGG GCT GGT T</td>
<td>CTT AAC CCC TCC TCC CAG AG</td>
<td>216</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>TTG GGC CTG TGT TAT CTC CT</td>
<td>GGG TCA GAG GCA AGC AGA G</td>
<td>198</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>TTC CTT ACT GCC TCT TGC TT</td>
<td>TGT CCT GCT TGC TTA CCT CG</td>
<td>189</td>
<td>55</td>
</tr>
<tr>
<td>9</td>
<td>CAC TTT TAT CAC CTT TCC TTG C</td>
<td>GAA AAC GGC ATT TTG AGT GT</td>
<td>173</td>
<td>55</td>
</tr>
</tbody>
</table>
p-53 translational research study

tumor samples collection. One hundred and seventy-six formalin-fixed samples from the primary tumor were collected between April 2000 and April 2001, corresponding to 54% of the clinical trial population (176 of 326 patients). Of the 176 samples, 127 were available for the purpose of the present study. The remaining 49 were previously used in the context of two other studies [6, 7]. Of the 127 samples, 108 were adequate for the purpose of p-53 gene evaluation by DHPLC (53 from patients treated with doxorubicin and 55 from patients treated with docetaxel). Hence, the percentage of patients from the clinical trial in which p-53 gene evaluation was feasible was 33% (108 of 326 patients).

representativeness of the p-53 study population. No statistically significant differences in terms of main patient characteristics (i.e. PS, number of metastatic sites, visceral involvement) were found between the group of patients participating in the p-53 study (108 cases) and the remaining group from the clinical trial (218 cases). Data are reported in Table 2.

p-53 gene status. Table 3 reports the rate of p-53 gene mutations detected from exon 5 to 9. One hundred and twenty-seven samples were available for the purpose of the p-53 study but in 19 samples (15%) p-53 gene evaluation was unfeasible because of technical reasons (i.e. DNA poor quality).

Table 2. Comparison between different patient cohorts

<table>
<thead>
<tr>
<th></th>
<th>p-53 population</th>
<th>Remaining population</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A N = 53</td>
<td>I N = 55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A N = 112</td>
<td>I N = 106</td>
<td></td>
</tr>
<tr>
<td>% pts Karnofsky</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS ≥ 80</td>
<td>79</td>
<td>85</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>% pts with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 sites</td>
<td>47</td>
<td>53</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>% pts with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>visceral mets</td>
<td>87</td>
<td>74</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>% RR</td>
<td>24</td>
<td>38</td>
<td>0.11 for A</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>52</td>
<td>0.13 for T</td>
</tr>
</tbody>
</table>

†overall comparison between the four subgroups.
A, doxorubicin; T, docetaxel; pts, patients; PS, performance status; mets, metastases; RR, response rate.

Table 3. Rate of p-53 gene mutations

<table>
<thead>
<tr>
<th>No. of evaluated cases</th>
<th>108</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases with mutations (by gene sequencing)</td>
<td>22/108 (20.3%)</td>
</tr>
<tr>
<td>No. of cases with mutations by exon</td>
<td>9/108 (8.3%)</td>
</tr>
<tr>
<td>Exon 5</td>
<td>6/108 (5.5%)</td>
</tr>
<tr>
<td>Exon 6</td>
<td>5/108 (4.6%)</td>
</tr>
<tr>
<td>Exon 7</td>
<td>2/108 (1.8%)</td>
</tr>
<tr>
<td>Exon 8</td>
<td>0/108 (0%)</td>
</tr>
</tbody>
</table>

DHPLC allowed for the identification of 73 of 108 adequate samples in which p-53 gene mutations could be possible. Of these, 13 and 21 samples had strongly aberrant or aberrant DHPLC curves which indicated p-53 gene mutations, while the remaining 39 samples had slightly aberrant DHPLC curves which did not allow excluding p-53 gene mutations. Accordingly, gene sequencing was carried out in all of the 73 cases screened by DHPLC. In all, 85% (11 of 13) of the strongly aberrant cases with DHPLC were confirmed to carry p-53 gene mutations by gene sequencing, while 52% (11 of 21) and 0% of the aberrant or slightly aberrant cases with DHPLC were confirmed as p-53 mutated by gene sequencing, respectively. These data indicate that DHPLC is an attractive screening tool, although confirmation by gene sequencing remains of critical importance to define p-53 gene status.

Of note, in patients carrying p-53 gene-mutated tumors no more than one mutation per case was observed.

A univariate analysis did not show any significant correlation between p-53 gene status and HER-2 status by fluorescent in situ hybridization, estrogen receptor (ER) status, and topo II α protein status, both evaluated by immunohistochemistry. HER-2, ER, and topo II α protein were centrally evaluated at the Pathology Department of the IJB. Moreover, no correlations were found between p-53 gene status and clinical variables (i.e. age, number of metastatic sites, visceral involvement, and PS). A full logistic regression model has been fitted for predicting p-53 status using as covariates age, PS, number of sites, visceral involvement, and PS. None of these variables had a significant impact on p-53 gene status.

interaction between p-53 gene status and response to the study drugs. Figure 1 reports objective response rates observed with either docetaxel or doxorubicin in the two different cohorts of p-53 gene-mutated and non-mutated cases. p-53 gene mutation seems to decrease the probability of response to doxorubicin [OR 0.55 (95 CI 0.10–2.89), P = 0.48] and to increase the probability of response to docetaxel [OR 1.81 (95 CI 0.46–7.22), P = 0.40], although these results do not reach statistical significance. When in a logistic regression model we enter p-53, treatment arm, and interaction

![Figure 1](image-url)
The results of the present study indicate that tumors carrying p-53 gene mutations might be less sensitive to anthracyclines than to taxanes. This observation is in line with preclinical data [1], although it seems that the predictive value shown by p-53 gene mutations in the present study is not strong enough to guide treatment decisions.

Two previous studies have evaluated the interaction between p-53 gene mutation and response to anthracyclines and taxanes [3, 4].

In the first of the two studies by Geisler et al. [3], 90 patients with locally advanced breast cancer were treated with weekly doxorubicin.

Although p-53 mutations in total were not significantly associated with progressive disease, p-53 mutations affecting or disrupting the L2/L3 domain and non-missense mutations predicted for resistance to doxorubicin [3]. Of note, the same group found similar findings in a second cohort of 35 breast cancer patients treated in the neo-adjuvant setting with 5-fluorouracil and mitomycin C [10].

In the second study by Kandioler-Eckersberger et al. [4], 67 locally advanced breast cancer patients were treated in a nonrandomized fashion with an anthracycline-based regimen or with paclitaxel (Taxol; Bristol-Myers-Squibb, NJ). Clinical responses to the anthracycline-based regimen were found to be dependent on normal p-53. Conversely, responses to paclitaxel were independent of p-53 gene status [4].

Our study differs from the two previously reported ones in the following three aspects: (i) patients have been randomly treated with either doxorubicin or docetaxel in the context of a phase III clinical trial; (ii) both cytotoxics have been delivered at full doses as single agents; and (iii) p-53 gene mutations have been investigated on a primary tumor sample although response to doxorubicin and docetaxel has been evaluated in the metastatic setting. Although the three studies present these differences, they all indicate that p-53 gene mutations may compromise sensitivity to anthracyclines but not to taxanes. More recently, an additional study has indicated that early breast cancer patients carrying p-53 gene-mutated tumors might be resistant to CMF adjuvant therapy, although the lack of a control arm makes the conclusion of this study uncertain [11].

Of note, the three studies evaluated p-53 gene status instead of p-53 protein. In the last few years, it has been shown that p-53 protein evaluation by immunohistochemistry does not necessarily correlate with p-53 gene mutations because not all gene mutations lead to increased protein levels detectable by immunohistochemistry [12]. In line with these data, in the present study we found that p-53 gene mutations had a poor level of correlation with protein levels measured by immunohistochemistry (data not shown).

Unfortunately, none of the three studies indicate that the predictive value shown by p-53 is strong enough to guide treatment decisions in clinical practice. Recently, it has been shown by Miller L et al. [13] that a 32-gene expression signature distinguishes p-53 mutant and wild-type tumors and outperforms sequence-based assessment of p-53 in predicting prognosis and therapeutic response in a series of 251 early breast cancer patients.

Moreover, the same study found that a subset of p-53 wild-type tumors expressed the mutant p-53 signature and presented an aggressive clinical behavior. In addition, some
tumors carrying p-53 gene mutations did not show the expected 32-gene signature and were correlated with a favorable clinical outcome [12]. These data indicate that although p-53 gene mutations are associated with a distinct gene expression profile, other factors may or may not confer a 'functional' p-53 status independently of p-53 gene mutations. For instance, p-53 target genes such as p21 and BAX are also directly regulated by the breast cancer oncogene c-Myc in a manner independent of p-53 [14,15].

More recently, it has been reported that p-53 codon 72 polymorphism may play a role in determining sensitivity or resistance to neo-adjuvant anthracycline-based regimens independently of gene mutations [16].

In a recently reported 'in vitro' study, the combination of codon 72 polymorphism and gene mutation data was shown to be a useful predictor of sensitivity to cytotoxics [17]. All this indicates that information on p-53 gene mutations has to be combined with other molecular parameters to better define the profile of tumors sensitive or resistant to anthracyclines.

In the present study, we have combined p-53 gene mutation data with topo II α protein levels evaluated by immunohistochemistry.

Topo II α protein levels are essentially a proliferation marker because topo II α plays a critical role in DNA replication [18].

Previous studies have shown a direct correlation between topo II α protein levels and Ki-67 immunostaining [19]. Moreover, it has been shown that in slowly proliferating tumors topo II α protein levels can be downregulated even in the presence of topo II α gene amplification [20]. In a previously reported study run by our group on the same series of patients presented in this manuscript, we showed that topo II α protein overexpression was associated with a substantial increase in the activity of doxorubicin, while docetaxel response rates were unaffected by topo II α protein levels [7]. This observation is in line with the concept that cytotoxics targeting different phases of the cellular cycle (nonphase-specific drugs such as anthracyclines) might be largely more active in highly proliferating tumors. Conversely, the activity of phase-specific drugs such as the taxanes might be less dependent on tumor proliferation status.

On the basis of the results of our previous study evaluating topo II α protein levels and response to doxorubicin and docetaxel [7], we hypothesized that tumors carrying a wild-type p-53 gene and a concomitant topo II α protein overexpression should derive the largest benefit from anthracyclines.

As expected, we found that the probability of response to doxorubicin increased by five-fold in the cohort of patients with wild-type p-53 and topo II α protein overexpression as opposed to the remaining group of patients presenting one or none of the two factors. Of note, the same interaction between p-53, topo II α protein, and response to docetaxel was not found.

Our findings need to be confirmed on a large number of patients. With this purpose, we are now evaluating the predictive value of p-53 gene mutations and proliferation status in a series of almost 1000 early breast cancer patients who have randomly been treated with an anthracycline-based or an anthracycline-docetaxel-based adjuvant therapy in the context of a phase III adjuvant trial. Another ongoing study coordinated by the European Organization for Research and Treatment of Cancer and run under the auspices of the Breast International Group (Principal Investigator H. Bonnefoi, Geneva, Switzerland) will play a major role in defining the predictive value of p-53 gene mutations in breast cancer patients randomly treated with anthracyline- or anthracycline/taxane-based therapies in the neo-adjuvant setting. This study is at present the only prospectively designed trial testing the predictive value of p-53 gene mutations on >1000 breast cancer patients. Interestingly, complementary DNA microarray analysis on primary tumor samples is also ongoing in the attempt to identify a gene profile predicting response to the evaluated chemotherapy regimens [21].

In conclusion, the present study shows that tumors carrying p-53 gene mutations might be less sensitive to anthracyclines than to taxanes. Nevertheless, the predictive value of p-53 gene status alone does not seem to be strong enough to support treatment decisions.

The evaluation of multiple molecular markers including p-53 and proliferation parameters might be more effective in predicting response to anthracyclines.

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references


