

**CORRELAÇÃO ENTRE A EXPRESSÃO DO GENE p53 E A
RESPOSTA À QUIMIOTERAPIA NEOADJUVANTE UTILIZANDO
PACLITAXEL E DOXORUBICINA EM CÂNCER DE MAMA
LOCALMENTE AVANÇADO (III-B)**

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À minha esposa Tânia e aos meus filhos Gabriel e Beatriz por
fazerem minha vida valer a pena.



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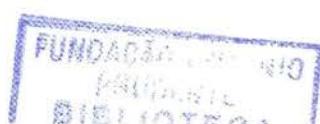
AOS MÉDICOS-RESIDENTES E TITULARES DO DEPTO. DE ONCOLOGIA CLÍNICA, por compartilharem a dura rotina de sucessos e fracassos no tratamento dos pacientes portadores de câncer.

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RESUMO

Agnaldo A. **Correlação da expressão do gene supressor de tumor p53 e a quimioterapia neoadjuvante em câncer de mama localmente avançado (III-B).** São Paulo;2000. [Dissertação de Mestrado – Fundação Antonio Prudente].

Introdução: O papel do gene supressor de tumor p53, modulando o processo de apoptose sugere que também possa afetar a eficiência de determinados agentes anti-neoplásicos. Conduzimos um estudo prospectivo não randomizado, avaliando o papel da expressão do p53 em mulheres portadoras de câncer de mama localmente avançado, submetidas a tratamento quimioterápico neoadjuvante com o regime formado por doxorubicina e paclitaxel.

Pacientes e Métodos: Foram avaliadas 60 pacientes do sexo feminino, que receberam três ciclos de quimioterapia neoadjuvante compreendida por 60 mg/m² de doxorubicina e 175 mg/m² de paclitaxel a cada 21 dias. Amostras representativas do tumor primário, provenientes da biópsia incisional pré-quimioterapia forma submetida à análise imunohistoquímica para avaliação da expressão do gene p53. As amostras classificadas como positivas foram também submetida à análise molecular através dos sequenciamento do DNA.

Resultados: Dentre as 60 pacientes analisadas, 12 (20%) expressaram positividade para p53. A taxa de resposta global com o regime quimioterápico foi de 86.6%, incluindo 40% de respostas clínicas completas e 18.3% de respostas completas anatomo-patológicas. O regime quimioterápico foi bem tolerado com uma incidência de náuseas e vômitos graus 2 e 3 de 17.7% e de 12.8% de leucopenia grau 3 e 4. A resposta à quimioterapia não foi relacionada com a expressão de p53. No entanto, pacientes classificadas como p53

negativas apresentaram uma maior possibilidade de obtenção de resposta completa anatomo-patológica ($p=0,317$ Chi-square).

Discussão: A combinação de paclitaxel e doxorubicina é altamente ativa em câncer de mama localmente avançado, no entanto a expressão do gene p53 não foi correlacionado com a resposta à quimioterapia, mas com uma tendência a obtenção de resposta completa anatomo-patológica. Deste modo, podemos concluir que a determinação da expressão do p53 pode ser utilizada para identificar pacientes que possam se beneficiar de tratamentos mais agressivos.

Descritores: Câncer de mama, p53/fator prognóstico, quimioterapia neoadjuvante, paclitaxel, doxorubicina.

SUMMARY

Introduction: The role of p53 in modulating apoptosis has suggested that it may affect efficacy of anticancer agents. We prospectively evaluated p53 alterations of 60 consecutive female patients with locally advanced breast cancer (III B) submitted to neoadjuvant chemotherapy.

Patients and Methods: Patients received three cycles of paclitaxel (175 mg/m^2) and doxorubicin (60 mg/m^2) every 21 days. Tumor sections prepared from the biopsy taken before treatment were analyzed immunohistochemically for altered patterns of p53 expression and samples classified as positive were also analyzed at the molecular level by DNA sequencing.

Results: An overall response rate of 86.6% was obtained, including 40% of clinical complete responses and 18.3% of complete pathologic responses. The chemotherapy regimen was well tolerated with 17.7% grade 2 and 3 nausea and 12.8% grade 3 and 4 leukopenia. Response to chemotherapy was not correlated with p53 expression, however there was a trend towards statistical significance when p53 expression was correlated to the obtention of a complete pathological response ($p=0.317$ chi-square).

Discussion: The combination of paclitaxel and doxorubicin is highly effective in locally advanced breast cancer, however the p53 status was not correlated with response to chemotherapy but with a trend to the obtention of complete pathological response. The p53 status may be used as a biological marker to identify those patients who would benefit from more aggressive treatments.

INTRODUÇÃO

A combinação de doxorubicina e paclitaxel tem sido testada em uma variedade de regimes e seqüências com a intenção de explorar o alto índice de respostas em câncer de mama metastático (HOLMES et al. 1999). Estudos iniciais demonstraram que a tolerabilidade da combinação era independente da seqüência pela qual o paclitaxel era infundido, em relação ao regime utilizado de doxorubicina (HOLMES et al. 1996). Com o intuito de utilizar a combinação como um regime ambulatorial, um estudo clínico foi realizado pelo Instituto Nacional de Câncer de Milão, que validou a hipótese de administração ambulatorial do regime e que sua tolerabilidade realmente não era dependente da seqüência pela qual as drogas eram administradas (GIANNI et al. 1995).

Muito embora as interações do paclitaxel com o cito-esqueleto sejam bem caracterizadas, os mecanismos moleculares pelos quais tais interações levam à cito-toxicidade não são bem compreendidas. Evidências recentes, sugerem que o paclitaxel altera determinados sinais de transdução intracelulares tais como a ativação de MAP kinase e a ativação transcripcional de genes que codificam para uma variedade de citoquinas (HORWITZ 1994; MOTWANI et al. 1999). O dano ao DNA ocasionado por uma série de quimioterápicos leva a um aumento da expressão do gene supressor de tumor p53, seguido pela parada das células em G1 e subseqüentemente apoptose. A proteína p53 é um regulador transcripcional multifuncional envolvido na resposta celular ao dano ao DNA e tem sido implicado como um potencial determinante da sensibilidade de tumores à agentes citotóxicos (DRANITSARIS et al. 1995; BONETTI et al. 1998; MILLER et al. 1990).

Conduzimos um estudo prospectivo não randomizado para investigar a eficácia e factibilidade do tratamento pré-operatório (neoadjuvante) constituído pela combinação de paclitaxel e doxorubicina em pacientes portadoras de câncer de mama localmente avançado

e o impacto da expressão do gene supressor de tumor p53 na taxa de resposta, sobrevida global e sobrevida livre de doença.

MATERIAL E MÉTODO

Entre Outubro de 1995 e Setembro de 1999, 60 mulheres diagnosticadas com tumores primários da mama, estadiadas clinicamente como localmente avançados (III-B – T4 N1-2 M0, de acordo com a classificação tumor, linfonodos e metástases – TNM) foram consecutivamente admitidas no estudo clínico. O tamanho mediano do tumor primário na população foi de 8,4 cm pelo exame clínico e pela mamografia. Todas as pacientes foram submetidas a uma biópsia incisional para confirmação histológica. O ensaio clínico foi previamente aprovado pela Comissão de Ética em Pesquisa do Centro de Tratamento e Pesquisa --Hospital do Câncer e todas as pacientes forneceram consentimento pós-informado.

Critérios de elegibilidade:

- Confirmação histológica de carcinoma ductal infiltrante
- Idade acima de 18 anos
- Índice de desempenho pela escala de Karnofsky acima de 90%
- Bilirrubina total < 0,5 mg/dl
- Creatinina sérica < 1,5 mg/dl
- Contagem absoluta de granulócitos > 1500/mm³
- Plaquetas > 100.000/mm³
- Função cardíaca adequada através de fração de ejeção acima de 50 %

Todas as pacientes realizaram mamografia bilateral antes do início do primeiro ciclo de quimioterapia e 3 semanas após o terceiro ciclo. A fração de ejeção foi mensurada antes do início do tratamento e 3 semanas após o terceiro ciclo.

Regime quimioterápico

Todas as pacientes foram pré-medicadas com glicocorticóides e bloqueadores dos receptores H1/H2 antes da infusão dos quimioterápicos. Doxorubicina foi administrada na dose de 60 mg/m^2 em infusão rápida, seguida pela infusão em 3 horas de paclitaxel (175 mg/m^2). Os ciclos de quimioterapia foram repetidos a cada 21 dias, mediante a recuperação hematológica. Após o terceiro ciclo de quimioterapia, todas as pacientes foram submetidas à mastectomia radical modificada com dissecção axilar. Após a recuperação do ato operatório, as pacientes receberam quimioterapia e hormonoterapia adjuvantes, de acordo com o número de linfonodos positivos na axila e da expressão dos receptores hormonais.

Avaliação da resposta tumoral

O tamanho do tumor primário foi determinado imediatamente antes da administração de cada ciclo de quimioterapia e antes da cirurgia. Antes do início da quimioterapia e na semana do tratamento cirúrgico todas as pacientes foram submetidas à mamografia bilateral. Em cada avaliação o produto dos dois maiores diâmetros foi utilizado para quantificar o tamanho tumoral. Na ausência de evidência clínica de tumor na mama, a resposta foi categorizada como resposta clínica completa (RCC). A diminuição do produto dos diâmetros em pelo menos 50% foi categorizada como resposta clínica parcial (RCP). Qualquer aumento tumoral após um mínimo de dois ciclos de quimioterapia

seria considerado como progressão clínica da doença. Os espécimes cirúrgicos foram analisados para a determinação da resposta anatomo-patológica, onde a ausência de células tumorais viáveis foi considerada como resposta anatomo-patológica completa.

Determinação da expressão do gene supressor de tumor p53

O método imunohistoquímico foi empregado em cortes histológicos preparados a partir da amostra da biópsia inicial. Os tecido foi fixado em formalina, posteriormente embebido em parafina e analisado pelo método imunohistoquímico para a identificação da alteração da expressão do gene supressor de tumor p53 pela técnica padrão de streptavidina-biotina. Foi utilizado o anticorpo monoclonal DO-7 (Dako, Co. Carpinteria CA) na diluição de 1: 100.

Os resultados foram interpretado por um único patologista, que não teve acesso aos dados clínicos das pacientes. Em cada caso, toda a amostra foi sistematicamente analisada por microscopia ótica em campo de 40X para a pesquisa da imunoreatividade de p53. Dentre todos os núcleos considerados como imunoreativos, somente aqueles claramente corados forma registrados como positivos para p53. Os tumores foram classificados como positivos ($> 20\%$ de núcleos positivos) ou negativos ($< 20\%$ de núcleos positivos).

As amostras classificadas como positivas foram posteriormente analisadas a nível molecular através do sequenciamento do DNA. Os blocos de parafina forma microdissecados e DNA genômico foi extraído. Foram desenhados *primers* flanqueando os domínios funcionais L2, L3 e a “loop-sheet-helix” e o DNA foi amplificado através da reação de cadeia de polimerase. O produto foi purificado e submetido a sequenciamento direto.

Foram utilizados os testes estatísticos de Chi-quadrado e teste exato de Fisher para a determinação das diferenças em proporções. As curvas de sobrevida foram realizadas pelo método de Kaplan-Meier e as diferenças entre os grupos pelo teste de log-rank. Diferenças foram consideradas como significantes com um $p < 0.05$.

CORRELATION OF P53 STATUS WITH OUTCOME OF NEOADJUVANT
CHEMOTHERAPY USING PACLITAXEL AND DOXORUBICIN IN STAGE III-B
BREAST CANCER

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Partial results were presented at the 1999 Meeting of the American Society of Clinical Oncology.

Submitted for publication

Cancer

Introduction

A combination of doxorubicin and paclitaxel has been tested in a variety of schedules and sequences to exploit the high therapeutic potential of the two drugs in metastatic breast cancer¹. Initial studies indicated that the tolerability of the combination was sequence dependent if paclitaxel was infused over at least 24 hours, independent of the schedule of doxorubicin administration². In order to use the combination as an outpatient treatment, a dose and sequence finding trial was performed at the National Cancer Institute of Milan. Taking advantage of safety and feasibility of short infusion of paclitaxel, the study showed that tolerability did not depend on sequence and that the combination was highly effective in metastatic breast cancer³.

Although the interactions of taxol with the cytoskeleton are well characterized, the molecular mechanisms by which such an interaction leads to cell cycle arrest and cytotoxicity are not well understood. Recent evidence suggests that taxol alters certain intracellular signal transduction events such as the activation of MAP kinase and transcriptional activation of genes encoding a number of cytokines^{4,5}. DNA damage caused by various chemotherapeutic agents leads to an increase in the level of tumor-suppressor gene p53, followed by a G1 cell cycle arrest, and subsequently apoptosis. The p53 protein is a multifunctional transcriptional regulator involved in the cellular response to DNA damage and has been implicated as a putative determinant of sensitivity of tumor cells to cytotoxic agents⁶⁻⁸.

We conducted a prospective, non-randomized trial to investigate the efficacy and feasibility of a combination of paclitaxel and doxorubicin as preoperative treatment for locally advanced breast cancer and the impact of the expression of the tumor-suppressor gene p53 on response rate, overall survival and disease-free survival.



Patients and Methods

Between October 1995 and September 1999, 60 women who had primary locally advanced breast cancer (IIIB - T4b N1-2 M0, according to the tumor, node, metastasis staging system) were enrolled in the trial. The median tumor size of this population was 8.4 cm by physical examination and mammography. All patients received an incisional biopsy to provide the histological diagnosis. The protocol was approved by the institutional Internal Review Board and all patients gave written, informed consent before entering the trial.

Patients were required to have histological proof of invasive ductal carcinoma, to be at least 18 years of age, have a performance status of 90% by the Karnofsky scale, have a serum bilirubin level < 0.5 mg/dl, serum creatinine level < 1.5 mg/dl, absolute granulocyte count $\geq 1500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$ and a normal cardiac function. All patients performed an ejection fraction test (MUGA scan) previous to the first cycle and 3 weeks after the third cycle of chemotherapy.

Treatment schedule

Following standard premedication with glucocorticoids and H1/H2 receptor blockers, doxorubicin (60 mg/m^2) was administered as a bolus infusion followed by paclitaxel (175 mg/m^2) infused over 3 hours. Chemotherapy was given every 3 weeks for three cycles. At the completion of chemotherapy all patients were submitted to a modified radical mastectomy with axillary dissection. After recovery of surgery, all patients

received systemic chemotherapy and adjuvant tamoxifen for five years when the estrogen receptor was positive. All patients underwent external beam irradiation using a 6 mV linear accelerator.

Evaluation of tumor response

The size of primary breast tumors was determined immediately before administration of each cycle of chemotherapy and before surgery. Before the first cycle and in the week before surgery, a mammography was performed. At each assessment, the product of the two greatest perpendicular diameters was used to quantify the tumor. In the absence of clinical evidence of tumor in the breast, response to therapy was categorized as a clinical complete response (cCR). When the clinical size of the breast tumor decreased by 50% or more, the response was judged to be partial response (cPR). When there was any increase in the size of the tumor after a minimum of two cycles of therapy, the patient was considered to have progressive disease (cPD). Surgical specimens were evaluated for their pathologic tumor status and were further classified as complete pathologic responders with no histologic evidence of invasive tumor cells (pCR) or with histologic evidence of invasive cells (pTC).

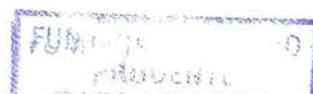
Determination of p53 status

Immunostaining was performed on histological sections prepared from the biopsy sample taken before treatment. Formalin fixed, paraffin embedded tissue sections were analyzed immunohistochemically for altered patterns of p53 expression, using a standard streptavidin-biotin technique. Sections (4 μ m thick) were deparaffinized in xylene, rehydrated in a graded ethanol series, and incubated in 3% hydrogen peroxide for 20

minutes. Specimens were then placed in a plastic Coplin jar containing citric buffer and heated in a microwave processor at 95° C. After the microwave processing, sections were left at room temperature for 30 minutes. Specimens were covered with normal goat serum for 15 minutes to reduce nonspecific staining and incubated with a 1:100 dilution of primary antibody D0-7 (Dako Co, Carpinteria CA) at room temperature overnight. Sections were washed with Tris-buffered saline, incubated with 1:100 dilution of biotinylated goat antimouse immunoglobulin G at room temperature for 30 minutes, and then covered with 1:100 dilution of streptavidin-biotin-peroxidase complex at room temperature for 30 minutes. The antibody was localized with 3,3'-diaminobenzidine tetrahydrochloride (DAB). Tissue sections were counterstained with Harris hematoxylin, dehydrated with ethanol, and mounted under a coverslip. Immunohistochemical staining of tumors with this antibody shows primarily a nuclear localization of p53 staining.

The staining results were interpreted independently by one pathologist who was unaware of the clinical outcome. In each case, the entire section was systematically examined under high-power fields (x 40) for p53 immunoreactivity. Among all immunoreactive nuclei, only those clearly immunostained were recorded as being p53 positive. The level of immunoreactivity was expressed as the percentage of p53 positive cancer cell nuclei. For analysis, tumors were classified in terms of p53 immunoreactivity as negative (< 20% positive nuclei) or positive (> 20% positive nuclei).

Samples classified as positive were also analyzed at the molecular level by DNA sequencing. Genomic DNA was extracted from paraffin blocks and sequences corresponding to the functional domains L2, L3 and the loop-sheet-helix of the p53 protein were amplified by polymerase chain reaction (PCR). DNA sequencing was performed using the ABI PrismTM 377 DNA Sequencer (Perkin-Elmer) and the DNA Sequencing Kit-



BigDye Terminator Cycle Sequencing (Perkin Elmer) as described elsewhere⁸. Patients were cross-classified by p53 expression and by clinical responses to chemotherapy.

For statistical analysis, differences in proportions were evaluated by the Chi-squared test or Fisher's exact test. Survival was estimated by use of Kaplan-Meier method, and differences between groups were tested by the log-rank test. For all statistical tests, differences were considered as significant at $p < 0.05$.

Results

Response to chemotherapy

All patients completed the planned three cycles of therapy and therefore were assessable for overall clinical local-regional tumor response. A clinical complete response (cCR) as previously defined of both breast and axilla was documented in 24 patients (40%). Twenty eight patients (46.6%) achieved a clinical partial response (cPR), resulting in an overall response rate to the regimen of 86.6%. We did not observe any cases of progressive disease during the treatment.

Pathologic examination of breast tissue from all 60 patients showed no evidence of residual cancer in 11 (18.3%) specimens and only noninvasive tumor (ductal carcinoma *in situ* [DCIS]) in 3 (5%) patients.

Toxicity

Chemotherapy was generally well tolerated. Alopecia was universal in all patients. In 180 delivered cycles, grade 2 and 3 nausea and vomiting was present in 17.7%, grade 3/4 leukopenia in 12.8%. Three patients required hospitalization and intravenous antibiotics

due to febrile neutropenia. No grade 3 or 4 mucositis was observed. There were no toxicity related deaths.

Forty-two patients (70%) had an altered ejection fraction after the three courses of chemotherapy, with a median drop of 6 points compared with the previous ejection fraction. Ten patients (16.6%) had a drop higher than 10 points in the ejection fraction test. No acute cardiotoxicity was observed. One patient developed cardiac insufficiency, requiring clinical intervention ten months after completion of treatment.

This relatively good tolerance to the drug regimen was reflected in the high relative dose intensity that could be achieved during the three cycles of primary chemotherapy with 93.3% of cycles being delivered on the scheduled date.

Correlation of p53 protein expression with response and survival

A high level of p53 immunoreactivity was seen in 12 of 60 patients (20%). Direct sequencing of these tumors, identified two mutations on codon 259, causing an aminoacid change from asparagine (GAC) to tyrosine (TAC). The response to chemotherapy was not correlated with p53 expression as shown in table 1. However there was a trend to statistical significance when p53 expression was correlated to the obtention of a complete pathological response. Eleven patients achieved a complete pathological response of whom, 10 were classified as p53 negative ($p=0.317$ chi-square). Figure 1 represents the overall survival of all patients regarding the p53 expression, showing no statistical correlation between survival and p53 expression ($p=0.765$ Log Rank). However the overall survival is dramatically changed among those patients who achieved a complete pathologic response as shown in figure 2, with a p value of 0.067 (Log Rank).

Discussion

Paclitaxel is one of the most promising anticancer agents for the therapy of breast cancer, where it has shown activity also in tumors refractory to doxorubicin treatment⁹. The combination of both drugs resulted in high response rates in metastatic disease, however with no impact in overall survival and in disease free survival¹⁰⁻¹². This combination has been previously used in the neoadjuvant setting by the Italian Group, who reported an overall response rate of 88 %¹³. Of note is that in this trial, only 41% of women were clinically staged as having locally advanced disease, favoring the high response rate in more initial stages. In our trial we achieved an overall response rate of 86.6%, including 18.3% of complete pathologic response, confirming the high efficacy of this regimen. It is, therefore, important to understand if there are cellular factors that can play a role in determining the response of breast tumors to the combination of paclitaxel and doxorubicin. The p53 protein plays a central role in the response to anticancer treatment. It has, in fact, been shown that in different cell types, the presence of a wild p53 induces a sensitization to DNA-damaging agents, although more recent evidence of a wild-type p53-induced chemo resistance has been described. Paclitaxel, which does not interact directly with DNA, was found to be able to activate p53 in some cell types, and this increase has been associated mainly with its ability to activate the raf-1 cascade.¹⁴ In other cell types, including one human ovarian cancer cell line, p53 expression was not increased after paclitaxel treatment, and the presence of a wild-type p53 did not result in change in sensitivity to paclitaxel in respect to cells expressing mutated p53¹⁵. Recently, the presence of wild-type p53 has been reported to decrease the cytotoxicity of paclitaxel (compared to the same cell lines not expressing wild-type p53). This was explained on the basis of a p53-dependent block in G1 after treatment that would prevent the cell from progressing to G2-M, where paclitaxel is known

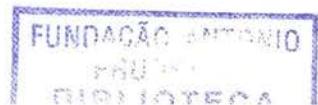
to exert its activity^{15; 16}. Another report, however, showed that in human ovarian cancer cell line, the disruption of wild-type p53 did reduce the cytotoxicity induced by paclitaxel¹⁷.

In our study, the response to chemotherapy was not correlated with p53 expression, but a trend to statistical significance was observed when the p53 expression was correlated to the odds of a complete pathological response. Since overall survival is dramatically changed among those patients who achieved a pathologic complete response, the determination of the p53 status may be used as a biological marker to identify those patient who would benefit from more aggressive treatments.

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Table 1 – p53 expression and response to neoadjuvant chemotherapy

	Clinical Response		Pathological response	
	Partial Response	Complete Response	Residual Tumor	Absence of tumor
P53 Negative	38	10	38	10
P53 Positive	10	2	11	1
Total	48	12	49	11
	P=0.747 Chi –square		P=0.317 Chi-square	

Figure 1 – Overall survival for all patients regarding the p53 gene expression.

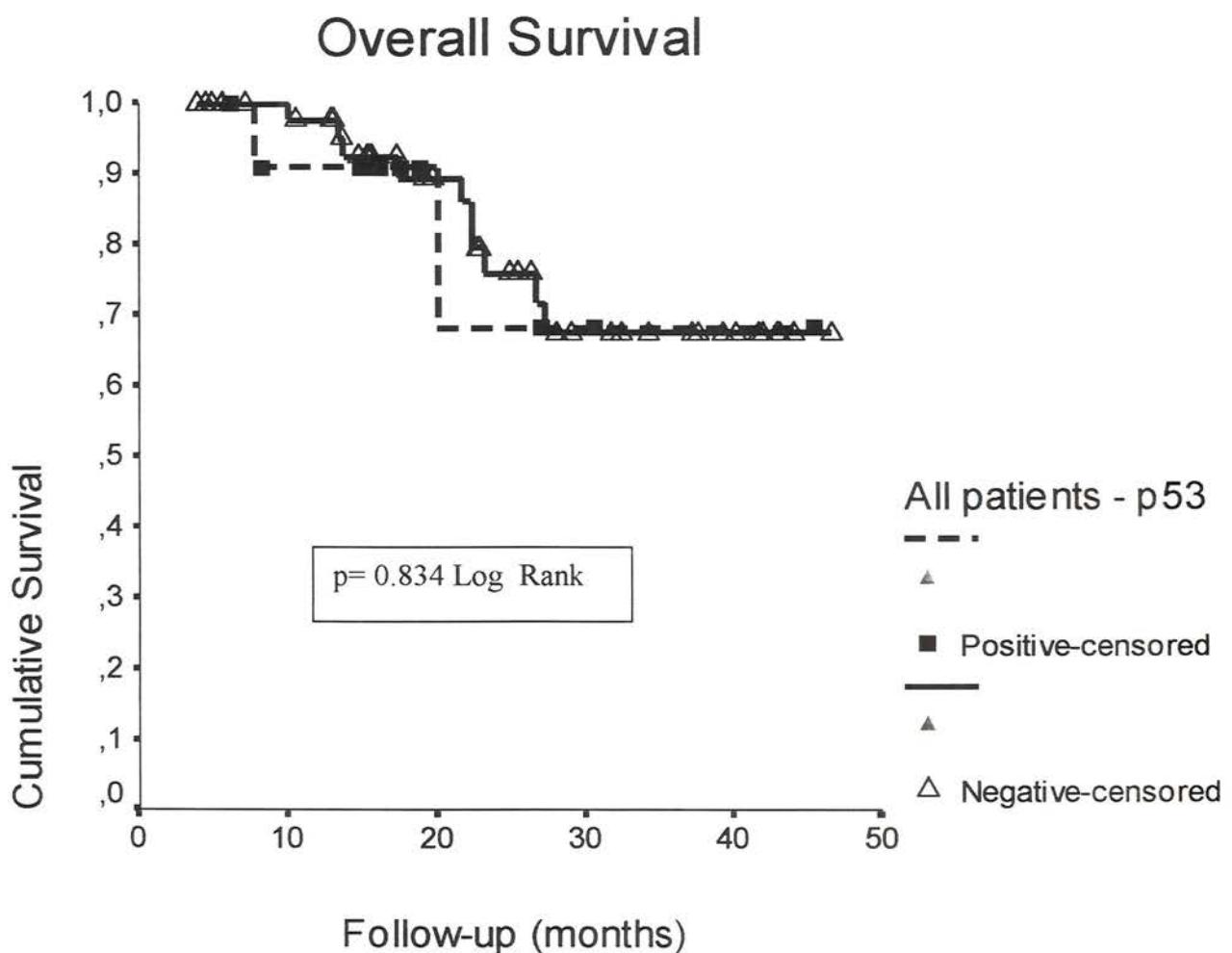
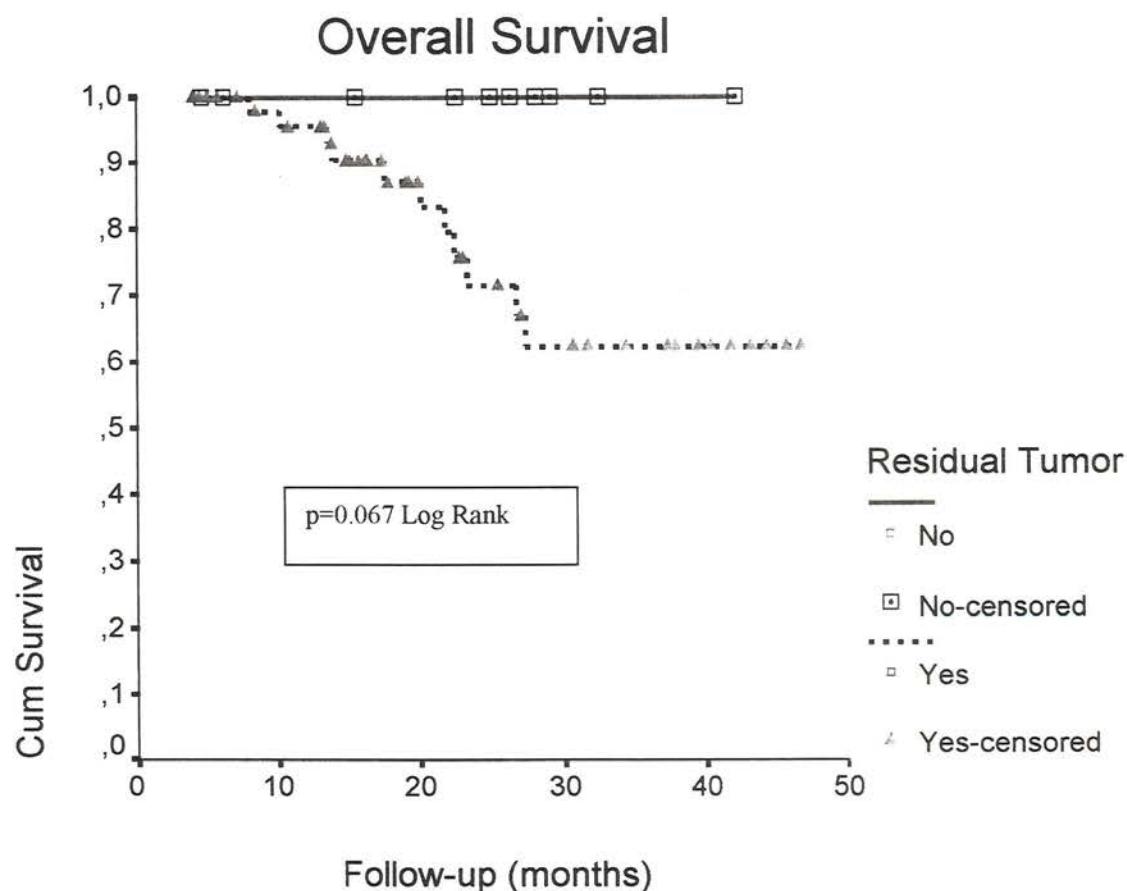


Figure 2. Overall survival for all patients and pathologic response.



DISCUSSÃO

Paclitaxel é uma das drogas mais promissoras no tratamento do câncer de mama, onde tem demonstrado atividade mesmo em pacientes portadoras de neoplasias resistentes à doxorubicina (GIANNI et al. 1994). A combinação das duas drogas resultou em um maior índice de respostas objetivas, mas sem impacto na sobrevida global em mulheres portadoras de câncer de mama metastático (HORTOBAGYI et al. 1997a; HORTOBAGYI et al. 1997b; SLEDGE et al. 1995). A combinação de doxorubicina e paclitaxel foi previamente testada pelo grupo italiano, que relatou uma resposta objetiva de 88% (MOLITERNI et al. 1997). No entanto é importante salientar que somente 41% destas mulheres eram realmente portadoras de doença localmente avançada, favorecendo o alto índice de respostas em tumores mais iniciais. Em nosso estudo, observamos um índice de resposta global de 86,6%, incluindo 18,3% de respostas completas anatomo-patológicas, confirmando assim a lata atividade desta combinação quanto utilizada em pacientes sem exposição prévia aos quimioterápicos.

Desta maneira, é importante determinar se existem e quais são os fatores celulares que influenciam à resposta celular a estes agentes quimioterápicos. A proteína do gene supressor de tumores p53, apresenta uma função central na resposta celular aos agentes quimioterápicos. De fato, tem sido demonstrado em diferentes tipos celulares que a presença do tipo não mutado de p53 induz a uma maior sensibilização do DNA aos agentes anti-neoplásicos, sendo no entanto descritos relatos de resistência a agentes quimioterápicos na mesma situação. A droga paclitaxel, que não interage diretamente com o DNA, foi relacionado com a ativação do gene p53 em determinados tipos celulares, e este aumento tem sido relacionado principalmente com a capacidade de ativação da cascata de ativação de raf-1 (BLAGOSKLONNY et al. 1995). Curiosamente em linhagens de

câncer de ovário, não existe esta ativação após o tratamento com paclitaxel, não havendo também relação entre a resposta à quimioterapia e a expressão do gene p53 (DEBERNARDIS et al. 1997) Recentemente, a presença do tipo não mutado de p53, foi relacionado com a diminuição da cito-toxicidade relacionada ao paclitaxel. Este fato tem sido justificado pelo provável bloqueio celular em G1 (fase dependente de p53), prevenindo as células de progredirem de G2 para M, onde encontra-se o momento de atividade do paclitaxel (DEBERNARDIS et al. 1997; WAHL et al. 1996). No entanto, em outro estudo, utilizando linhagens celulares de câncer de ovário, a presença de p53 mutado diminuiu a cito-toxicidade induzida por paclitaxel (WU et al. 1996).

CONCLUSÕES

Em nosso estudo, a resposta à quimioterapia não foi correlacionada com a expressão de p53, mas uma tendência estatisticamente significativa foi observada com a possibilidade de obtenção de resposta completa e a expressão normal de p53. Uma vez que a sobrevida global é dramaticamente modificada entre aquelas pacientes que obtém resposta anatomopatológica completa, a determinação da expressão de p53 pode ser utilizada como um marcador biológico para identificar aquelas pacientes que se beneficiariam de tratamentos pré-operatórios mais agressivos.

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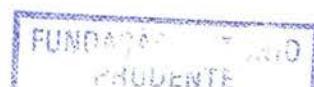
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