**SUMMARY**

**Objective.** The 21-gene expression assay may support the decision regarding use of chemotherapy in early breast cancer. We sought to investigate the potential impact of incorporating the 21-gene expression assay into private practice in Brazil, from the perspective of third party payers.

**Methods.** We conducted a web-based survey with 30 (of a total of approximately 700) Brazilian medical oncologists, who were stratified by State according to the proportion of patients with breast cancer and private health insurance. We evaluated the possible treatment of first choice for patients with lymph-node-negative, estrogen-receptor-positive breast cancer, regardless of menopausal status. Interviewees were not aware of the objective of the study. Responses permitted a quantitative assessment of the care patterns regarding use of different chemotherapy regimens, type of premedication, use of growth factors, and use of intravenous antibiotics for febrile neutropenia. We calculated medication costs using the manufacturer’s recommended prices. Other direct medical expenses, indirect medical costs, and non-medical costs were not included.

**Results.** Considering a hypothetical cohort of 100 patients without access to the 21-gene expression assay, the survey showed that 84 patients would receive chemotherapy. Reclassifying patient eligibility for chemotherapy according to the 21-gene expression assay would lower this number to 49. For a hypothetical cohort of 100 patients with access to the test, US$ 79,361.43 would be saved in main direct medical costs. Such results, however, would greatly vary according to tumor size: the 21-gene expression assay could increase direct medical costs in T1 tumors, and decrease costs in cases with T >2 cm.

**Conclusion.** Considering the current price for the 21-gene expression assay in Brazil, our economic analysis suggests that such testing is an overall cost-saving, from the perspective of third party payers. Further, optimal use of resources would entail targeted use of the 21-gene expression assay.

**KEY WORDS:** Breast neoplasms. Drug therapy. Gene expression.

**INTRODUCTION**

With nearly 1.2 million new cases diagnosed every year, breast cancer is by far the most frequent type of tumor in women, worldwide. In Brazil, breast cancer is not only the most frequent non-cutaneous tumor but also the most lethal. Despite high incidence, breast cancer is curable in the majority of women when diagnosed at early stages, with adjuvant systemic therapy playing a prominent role in achieving long-term disease control and cure. Indication of chemotherapy has historically been based on clinical and pathologic parameters such as age, tumor size and lymph-node involvement. Chemotherapy is typically indicated for women of 70 years of age or less, with tumors 1 cm or more in diameter or with positive axillary nodes; furthermore, chemotherapy may be considered for tumors between 0.6 cm and 1 cm. On the other hand, chemotherapy may be avoided in cases with good prognostic features and when there is tumor expression of hormone receptors. In such patients, hormone therapy with tamoxifen alone may reduce risks of recurrence by near half.

There is growing interest in use of prognostic tools based on molecular features of early breast tumors. Of the several gene-signature tools developed recently, the 21-gene expression assay is currently at the more advanced stages of validation and clinical use. The assay is based on quantitative reverse-transcription polymerase chain reaction (qRT-PCR) analysis of RNA extracted from formalin-fixed, paraffin-embedded tumor tissue. A recurrence score is computed using an algorithm that provides...
the level of expression of 16 breast cancer-related genes and five reference genes for each tumor sample. The 21-gene expression assay was initially validated with 668 tumor blocks from patients who received tamoxifen in the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-14, which compared this drug with placebo in patients with negative axillary nodes and estrogen-receptor-positive breast cancer. Proportions of patients in the low, intermediate, and high risk categories were 51%, 22%, and 27%, and Kaplan-Meier estimates of distant recurrence rates at 10 years were 6.8%, 14.3%, and 30.5%, respectively in these groups. In a second study, the 21-gene panel was performed in tumors from 651 patients included in the NSABP B-20 trial, which compared tamoxifen alone or combined with chemotherapy in axillary-node negative and estrogen-receptor-positive breast cancer. In this study, there was a statistically significant correlation between the recurrence score and benefit from chemotherapy in terms of 10-year distant disease-free survival: patients with high-risk tumors had great benefit from such treatment, whereas patients with low risk derived minimal, if any, benefit (in patients with intermediate-risk tumors, uncertainty of estimates did not exclude a clinically important benefit). The 21-gene expression assay has thus become an ancillary tool for decisions regarding the use of chemotherapy among patients with axillary-node-negative, estrogen-receptor-positive breast cancer, especially for tumors with more than 0.5 cm and negative expression of HER-2. Withholding chemotherapy in patients without an expected benefit from this treatment might spare them from toxicity and could represent a savings for society. Indeed, previous studies have suggested that using the 21-gene expression assay is a cost-saving from the perspective of US medicine. In the present study, we sought to investigate the potential impact of incorporating the 21-gene expression assay in Brazil, from the perspective of private practice.

**METHODS**

**Overview of the study design**

In order to examine the potential impact of incorporating the 21-gene panel in Brazil, we built a model based on the patterns of care for axillary-node-negative, estrogen-receptor-positive, early breast cancer. This model was based on the results of a survey conducted with medical oncologists working in private practice, as well as on data from the relevant literature. The model followed the perspective of private third party payers, and incorporated only the direct medical expenses associated with treatment. The model allowed us to estimate treatment costs in two hypothetical cohorts of 100 patients, one cohort with and another without access to the 21-gene panel.

**Survey with medical oncologists**

We began by conducting a web-based survey with 30 (out of a total of approximately 700) Brazilian medical oncologists, who were invited by one of the authors by telephone and not aware of the study objective. The medical oncologists represented states and cities where approximately 80% of new breast cancer cases are diagnosed each year in Brazil. In addition, the number of interviewees per state followed the same proportion of patients with private health insurance in Brazil. The questionnaire consisted of case vignettes presenting different clinical scenarios aiming to investigate the treatment of first choice for patients with axillary-node negative, estrogen-receptor-positive, early breast cancer, regardless of menopausal status. Each vignette presented a case with one of the tumor sizes of interest: \( T = 0.6-1 \) cm with adverse features (angiolymphatic invasion, high nuclear grade or high histologic grade), \( T = 1.1-2.0 \) cm, \( T = 2.1-4.0 \) cm, and \( T > 4.0 \) cm. In other words, the four case vignettes consisted each of a woman with axillary-node negative, estrogen-receptor-positive breast cancer, but information on the tumor size varied among the four cases and was presented as the range in cm shown above. Responses allowed a quantitative assessment of the care patterns regarding chemotherapy regimen for each of the four tumor sizes. In addition, we assessed interviewees’ preferences regarding the type and dose of antiemetic premedication used in each case, the dose and duration of use of granulocyte-colony-stimulating factor (G-CSF) and antibiotics for in-hospital treatment of febrile neutropenia, should it develop. Surveys were conducted between November 2007 and January 2008.

**Source of data for economic analyses**

Brand-name medication and the 21-gene expression assay costs were calculated using the manufacturer’s recommended prices at the exchange rate of 1.7. Direct medical expenses assessed in the study were costs of chemotherapy, antiemetic premedication, prophylactic or therapeutic G-CSF, and antibiotics for in-hospital treatment of febrile neutropenia. Other direct medical costs, indirect medical costs, and non-medical costs were not considered in the model. We estimated costs for the two hypothetical cohorts of 100 patients using the stage distribution and recurrence score results reported by Paik et al. This stage distribution is as follows: \( T \leq 1 \) cm, 16% of cases; \( T = 1.1-2.0 \) cm, 46%; \( T = 2.1-4.0 \) cm, 33%; and \( T > 4.0 \) cm, 5%. Table 1 shows medication costs for each chemotherapy regimen assessed in the

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Medication costs (US$)</th>
<th>Rate of febrile neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF (oral C, 6 cycles)</td>
<td>382.67</td>
<td>0.3%21</td>
</tr>
<tr>
<td>CMF (intravenous C, 9 cycles)</td>
<td>565.81</td>
<td>0.3%*</td>
</tr>
<tr>
<td>CMF (intravenous C, 6 cycles)</td>
<td>377.21</td>
<td>0.3%*</td>
</tr>
<tr>
<td>AC (4 cycles)</td>
<td>1,493.98</td>
<td>0.9%21</td>
</tr>
<tr>
<td>FAC (6 cycles)</td>
<td>1,596.48</td>
<td>4.4%22</td>
</tr>
<tr>
<td>FEC100 (6 cycles)</td>
<td>4,044.13</td>
<td>8.4%23</td>
</tr>
<tr>
<td>AC (4 cycles) + P (4 cycles)</td>
<td>16,814.92</td>
<td>3%24</td>
</tr>
<tr>
<td>AC + P (dose dense)</td>
<td>16,814.92</td>
<td>3%**</td>
</tr>
<tr>
<td>DC (4 cycles)</td>
<td>17,328.99</td>
<td>5%25</td>
</tr>
<tr>
<td>FEC100 (3 cycles) + D (3 cycles)</td>
<td>21,392.29</td>
<td>11.2%23</td>
</tr>
<tr>
<td>FEC90 (4 cycles) + P (8 weekly cycles)</td>
<td>23,123.57</td>
<td>5.1%26</td>
</tr>
<tr>
<td>AC (4 cycles) + D (4 cycles)</td>
<td>27,320.94</td>
<td>16%27</td>
</tr>
<tr>
<td>DAC (6 cycles)</td>
<td>27,376.45</td>
<td>24%22</td>
</tr>
</tbody>
</table>

A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; F, fluorouracil; P, paclitaxel.
* Rates for intravenous CMF assumed to be equivalent to that of oral CMF.
** Rate for dose-dense regimen assumed to be the same as for AC + P.21
model, along with incidence of febrile neutropenia associated with the regimens according to literature.²¹⁻²⁷ Types and doses of antiemetics, G-CSF and antibiotics were obtained from the survey with medical oncologists.

**The model and its assumptions**

In each subgroup of patients defined by tumor size in the hypothetical cohort with no access to the 21-gene expression assay, the proportion of patients receiving chemotherapy, as well as regimens used in each subgroup, were derived from the survey with medical oncologists. Our model assumed that patients with access to the 21-gene expression assay would receive chemotherapy if their recurrence score was intermediate or high, whereas patients with a low score would not receive chemotherapy. In addition, we assumed that T1a and low-risk T1b patients would not receive chemotherapy among those without access to the 21-gene expression assay. In order to estimate treatment costs in the hypothetical cohort with access to the 21-gene expression assay, the relative distribution of chemotherapy regimens that would be used in each subgroup defined by tumor size was assumed to be identical to the distribution obtained in the survey.

**Subgroup and sensitivity analyses**

We hypothesized that the economic impact of using the 21-gene expression assay would vary according to the baseline risk of recurrence in each subgroup of patients defined by tumor size, the price of the test and eventual reductions in chemotherapy drug prices. Therefore, we conducted separate analyses in each subgroup of risk, as well as sensitivity analyses that took into account varying prices for chemotherapy and the assay.

**RESULTS**

**Use of medications**

Considering two hypothetical cohorts of 100 patients, the survey with medical oncologists indicated that 84 patients would receive chemotherapy if the 21-gene expression assay was not available. Of note, 43% of patients with tumors measuring between 0.6 and 1 cm and with adverse features would not receive chemotherapy in the cohort with no access to the 21-gene expression test. Reclassifying patients on the assumption that the 21-gene expression assay was available and that it would indicate chemotherapy led to the prediction that 49 patients would receive chemotherapy. The percentages of patients in each subgroup of tumor size that would receive chemotherapy in the two hypothetical cohorts are: in the cohort with no access to the 21-gene expression assay, 5%, 41%, 33%, and 5% of patients receiving chemotherapy would belong to categories of tumor size 1.0 cm or less, 1.1 to 2.0 cm, 2.1 to 4.0 cm, and more than 4.0 cm, respectively. Corresponding figures in the cohort with access to the assay were 7%, 23%, 16%, and 3%.

For each tumor size category, the survey indicated a series of chemotherapy regimens that could be used. The regimens most frequently used in each category were: T ≤1 cm, four cycles of doxorubicin and cyclophosphamide (AC); T =1.1-2.0 cm, there was a tie between fluorouracil, epirubicin and cyclophosphamide (FEC100) and fluorouracil, doxorubicin and cyclophosphamide (FAC), both for six cycles; T =2.1-4.0 cm, six cycles of FEC100; and T >4.0 cm, six cycles of FEC100.

With regard to use of antiemetics and prophylactic G-CSF, the survey indicated a preference for intravenous treatment of febrile neutropenia as follows: cefepime (63%), ceftazidime (13%), ceftazidime plus an aminoglycoside (7%), ceftazidime plus vancomycin or teicoplanin (3%), and imipenem or meropenem (3%).

**Expected incidence of febrile neutropenia**

In the hypothetical cohort of 100 patients with no access to the 21-gene expression assay, the overall expected incidence of febrile neutropenia, according to tumor size distribution used in the model and stage-weighted use of each regimen, would be 5.1%. In a hypothetical cohort with access to the 21-gene expression assay, this incidence would be 2.8%.

**Treatment costs**

Table 2 displays the medical costs estimated for treating the two hypothetical cohorts of 100 patients, along with the stage-weighted average cost for treating one patient in each cohort. For a hypothetical cohort of 100 patients with access to the 21-gene expression assay, approximately US$ 79,400.00 would be saved in main direct medical expenses, despite cost of the assay. Sparing patients from unnecessary administration of chemotherapy drugs, as suggested by the 21-gene expression assay, accounted for the largest direct saving in our model. By itself, this reduction would be enough to cover the 21-gene expression assay costs as well as save more than US$ 33,000.00. Medications for prophylaxis and treatment of chemotherapy side effects accounted for 18% of the cost difference between the two hypothetical cohorts.

**Subgroup and sensitivity analysis**

In an attempt to identify possible subgroups of patients in which the 21-gene expression assay would result in the greatest saving of direct medical costs, we recalculated expenses by dividing patients into groups according to tumor size. As shown in Table 3, savings would be greater in patients with tumor size >2.0 cm. On the other hand, for patients with T1 tumors, our model indicates that using the 21-gene expression assay would actually increase direct expenses.

Sensitivity analysis indicated that, to achieve the same costs for patients with T1 tumors in the two hypothetical cohorts, a 46% reduction in the price of the 21-gene expression assay would be required. If this price reduction was applied only to patients with T1 tumors, the model indicated that the average cost of the 21-gene expression assay would have to be 28% lower, increasing overall savings for the entire cohort to almost US $143,600.00.

Lastly, we examined how a possible reduction in chemotherapy...
drug prices would affect our model. This sensitivity analysis suggested that using the 21-gene expression assay would continue to be a cost-saving approach in the case of chemotherapy price reductions up to 30%. Using the 28% lower price for the 21-gene expression assay, as suggested earlier, application of the test would still be cost-saving if chemotherapy prices were reduced by 56%.

**Discussion**

Results of our study suggest that the 21-gene expression assay would be a cost-saving in Brazil, from the perspective of third-party payers and considering the current price for the exam in Brazil. However, results also suggest that testing could actually increase direct medical costs in patients with lymph-node negative, estrogen-receptor-positive T1 tumors, and reduce costs in patients with tumor size >2 cm. Thus, our data confirm previous predictions of overall cost-savings in the US health care scenario. It is the first study, to our knowledge correlating expected savings with tumor size.17, 18

Chemotherapy plays a central role in the adjuvant treatment

of women with early breast cancer.4 However, the opportunity to avoid chemotherapy in cases with no expected benefit from such treatment may decrease overall toxicity of adjuvant therapy and optimize use of resources. This is especially true among patients with estrogen-receptor-positive tumors where tamoxifen reduces risk of recurrence by approximately half, in comparison with observation.3 In premenopausal patients, aromatase inhibitors may further reduce risk of recurrence, when compared with tamoxifen.28-31 Recently, results of the 21-gene expression assay have been shown to correlate with outcome in postmenopausal women treated with anastrozole,32 and further data on the benefit from adjuvant chemotherapy in this patient population are eagerly awaited.33 It should be noted that the recurrence score, whose results are categorized using the arbitrarily chosen subgroups with a low, intermediate, or high risk in terms of 10-year distant disease-free survival, is in fact a quantitative variable whose value may range from 0 to 100, and whose correlation with outcome also displays a continuous relation.33 The chief limitation of our study is the hypothetical nature inherent to economic models such as this one. Our model included the main financial costs associated with adjuvant therapy for breast cancer, but many other direct costs, as well as indirect costs, were not taken into account by the model. In addition, the effectiveness of therapy based on risk prediction by the 21-gene expression assay was not considered in the model. Other economic models currently available have also been limited to cost analyses, and have not taken effectiveness into account.17, 18 That is why, prospective trials, such as the TAILORx, validating chemotherapy decisions based on the 21-gene expression assay in intermediate-risk patients, are expected.34 Until such results are available, using the recurrence score to avoid chemotherapy is based on retrospective data suggesting that this treatment is not beneficial in the subgroup of patients with axillary-node-negative, estrogen-receptor-positive breast cancer and a low recurrence score.35

Another limitation of our economic model includes variability of definition and how the incidence of febrile neutropenia was calculated in the original trials of different chemotherapy regimens. Reports of this adverse event are not standardized in literature, with some authors estimating incidence on the basis of total number of cycles, while others use the total number of patients in the denominator. In some cases, the rate of febrile neutropenia was not available, and we used as a proxy for this rate the incidence of grade 4 neutropenia or incidence of neutropenia with a similar regimen. Finally, this study is limited by our inability to supply the model with Brazilian estimates for stage distribution upon diagnosis of breast cancer. The very few previous attempts to investigate this distribution in Brazil were made in the public sector, where currently there is no coverage nor is any anticipated in the near future, for the 21-gene assay.

One issue that was not addressed in the current study, where interviewees were unaware of the survey goal, is that knowledge about results of the 21-gene expression assay may influence the physician’s prescription practice, not only about indicating or foregoing chemotherapy, but also in terms of the type of chemotherapy chosen. In other words, it is conceivable that physicians would indicate chemotherapy regimens associated with greater relative benefits, in terms of reducing risks of recurrence and death, should they be aware that a patient’s
Procuramos investigar o impacto potencial da incorporação ao uso de quimioterapia (QT) no câncer de mama precoce. como painel de 21 genes, pode apoiar decisões com relação a:

Conflict of interest: none

decisions based on the recurrence score are urgently needed. savings are expected to be greater. Further studies are required to enhance our understanding of the role of the 21-gene expression assay in actual practice, and validation of chemotherapy decisions based on the recurrence score are urgently needed.

Conflict of interest: none

RESUMO

Potencial impacto econômico do painel de expressão de 21 genes no tratamento adjuvante do câncer de mama no Brasil

Objetivo. O índice de recorrência (IR), também conhecido como painel de 21 genes, pode apoiar decisões com relação ao uso de quimioterapia (QT) no câncer de mama precoce. Procuramos investigar o impacto potencial da incorporação do IR na prática privada no Brasil, a partir da perspectiva das fontes pagadoras.

Métodos. Conduzimos uma pesquisa com 30 oncologistas brasileiros (de um total de aproximadamente 700), que foram estratificados por Estado de acordo com a proporção de pacientes com câncer de mama e com cobertura pelo sistema de saúde suplementar. Avaliamos o tratamento de primeira escolha para pacientes com câncer de mama com axila negativa e expressão positiva do receptor de estrógeno, independente do estado menopausal. Os entrevistados não estavam cientes do objetivo do estudo. As respostas permitiram uma avaliação quantitativa dos padrões de cuidado, considerando o uso de diferentes regimes de QT, o tipo de pré-medicacións, o uso de fatores de crescimento e o tratamento hospitalar da neutropenia febril. Calculamos o custo dos medicamentos usando o Brasisíndice, e o custo do IR foi fixado em R$ 3.900,00 (MammaGene®). Outras despesas médicas diretas, custos médicos indiretos e custos não-médicos não foram considerados.

Resultados. Numa corte hipotética de 100 pacientes sem acesso ao teste de IR, 84 iriam receber quimioterapia. Reclassificando a elegibilidade das pacientes para QT de acordo com o IR, esse número caíria para 49. Para uma corte hipotética de 100 pacientes com acesso ao IR, seriam economizados R$ 134.915,00 em despesas médicas diretas.

Conclusão. Considerando o preço atual para avaliação do IR no Brasil, nossa análise económica sugere que este teste economizaria custos, pela perspectiva das fontes pagadoras do setor privado. Além disso, o uso otimizado de recursos poderia requerer o emprego do painel de 21 genes de forma racional.

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