A Study of the Impact of the 21-Gene Breast Cancer Assay on the Use of Adjuvant Chemotherapy in Women with Breast Cancer in a Mexican Public Hospital

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Background: The majority of breast cancer patients in Mexico are treated through the public health system and >80% receive adjuvant chemotherapy. The aim of this prospective study was to characterize the impact of the Oncotype DX assay on adjuvant therapy decision making and the confidence in those decisions amongst public sector physicians in Mexico.

Methods: Ninety-eight consecutive patients with ER+, HER2−, stage I–IIIa, N0/N1-3 node-positive breast cancer from the Instituto Nacional de Cancerología were eligible for the study. The primary endpoint was the overall change in treatment recommendations after receiving the assay results.

Results: Of 96 patients, 48% received a chemohormonal therapy recommendation prior to testing. Following receipt of results, treatment decisions changed for 31/96 (32%) patients, including 17/61 (27%) node-negative patients and 14/34 (41%) node-positive patients. The proportion of patients with a chemotherapy-based recommendation decreased from 48% pre- to 34% post-assay (P = 0.024). 92% of physicians agreed that they were more confident in their treatment recommendation after ordering the assay.

Conclusions: These results suggest that use of the 21-gene assay in the Mexican public health system has a meaningful impact on adjuvant treatment recommendations that may reduce the overall use of chemotherapy.

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KEY WORDS: Oncotype DX; Recurrence Score; decision impact

INTRODUCTION

Breast cancer incidence in Mexico has risen over the past few decades; a 2010 estimate showed that the annual risk has increased from 2.2% to 4.6% over the past 30 years, affecting both lower and higher socioeconomic demographics [1]. In Mexico, patients access treatment through the public health system, which is comprised of Social Security-funded institutions and those that are funded through other means, and covers approximately 70% of the population [2].

The majority of Mexican women diagnosed with breast cancer are first detected at an advanced stage, primarily due to lack of education and public awareness and access impediments to proper screening facilities and resources [3]. An analysis from the Mexican Ministry of Health indicated that only 10% of patients presented with stage I disease [4]. In some reports, including a large study from the National Cancer Institute of Mexico in 2007 [5], more than 80% of newly diagnosed breast cancer patients presented with locally advanced or metastatic disease.

In Mexico, approximately 60–90% of early stage hormone receptor-positive, HER2−negative patients are treated with chemotherapy [6,7] and within the public health system, an estimated 80% of breast cancer patients treated receive adjuvant chemotherapy [3]. Not all breast cancer patients derive the same benefits from adjuvant chemotherapy [8], yet, despite this, most of the patients with breast cancer in Mexico receive it. A high use of adjuvant chemotherapy carries with it costs in terms of adverse effects on the patients and resource consumption burdens to the health care system [9].

The Oncotype DX® Breast Cancer Assay is a genomic assay based on the measurement of the expression of 21 genes related to prognosis and chemotherapy benefit. The test yields a Recurrence Score® result that is prognostic for breast cancer recurrence out to 10 years and predicts the likelihood of benefit from chemotherapy in women with newly diagnosed, early stage, ER–positive invasive breast cancer. The assay is performed on a formalin-fixed paraffin-embedded core biopsy or surgery tumor sample, ideally prior to adjuvant treatment decision making. To date, considerable experience has been garnered using the Oncotype DX assay and its use is incorporated into several major treatment guidelines to predict adjuvant chemotherapy benefit in ER-positive, HER2−negative early stage breast cancer [10–13].

Multiple studies have shown that use of the Oncotype DX Breast Cancer Assay affects treatment recommendations [14–26]. These studies demonstrated that analysis of treatment decisions before and after receipt of Recurrence Score information showed approximately a 30% decrease in the percentage of patients receiving chemotherapy.

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in chemotherapy recommendations [27]. In addition, several of these studies have also demonstrated an increase in physician and patient confidence in the treatment decision following receipt of the assay result.

In Mexico, the Oncotype DX Breast Cancer Assay has been utilized primarily within the private health system where one recent study showed that use of the assay changed treatment decisions in 57% of patients [28]. There are no data that describe the potential impact of the assay on adjuvant treatment decision-making for patients treated in the public sector where patient demographics and socioeconomic factors are different and decision making is by consensus agreement of a committee composed of oncologists, surgeons, and pathologists. The primary objective of this study was to characterize the impact of the Recurrence Score result on the adjuvant therapy decision-making process from a committee perspective in the public sector patient demographic. In addition, physician confidence in treatment decisions pre- and post-assay was assessed.

METHODS
Study Design

This prospective study was conducted at the National Cancer Institute, Secretariat of Health (Instituto Nacional de Cancerología, SSA) in Mexico City. Physicians eligible to participate were part of a multi-disciplinary team of physicians, surgeons, pathologists, and health care providers that treat breast cancer. The protocol for this study was approved by the Instituto Nacional de Cancerología Bioethics Committee Institutional Review Board. Genomic Health Inc. provided the assays at no cost to the patient or health care system.

Eligible patients had tumors that were identified as estrogen receptor positive (ER+), HER2 negative (HER2−) by local pathology (IHC and/ or FISH), and had 0–3 positive lymph nodes. In addition, eligible patients had adequate performance status (ECOG ≤ 1 or Karnofsky ≥ 70) and no contraindications to receiving systemic chemotherapy. All subjects were ≥18 years of age, non-metastatic, and provided informed consent prior to enrollment into the study. Patients were excluded if their tumor sample failed to meet the established pathology guidelines from the Genomic Health, Inc. laboratory.

Consecutive eligible patients were asked to join the study by their oncologist between May 2011 and March 2012. After enrollment, the multi-disciplinary team completed an evaluation of the case and made a treatment recommendation via consensus discussion of hormonal therapy (HT), combined chemohormonal therapy (CHT), or chemotherapy (CT) without a hormonal therapy component. For this initial treatment recommendation, the team was asked to take into account conventional clinical–pathological factors and patient input. Following documentation of the recommendation, a pre-assay questionnaire was completed by the attending physician to document the initial recommendation. Following the initial evaluation, the Oncotype DX Breast Cancer Assay was ordered. After receiving the results of the assay, the multidisciplinary team re-evaluated the treatment recommendation and documented any change to the original recommendation. The attending physician then completed the post-assay questionnaire. Finally, the attending physician was asked to assess his/her confidence in the treatment decision after ordering the assay.

Statistical Analyses

The primary endpoint was the rate of changed treatment recommendations, comparing the recommendations made in accordance with the customary guidelines to the recommendations made after receiving the results of the assay. The study was designed to accrue 100 patients, including both node-negative (N0) and node-positive (N+) patients.

The proportions of treatment recommendations that changed from pre-assay to post-assay were calculated, along with 95% confidence intervals. McNemar’s test was used to assess whether the proportion of patients who received a treatment recommendation for chemotherapy changed after the Oncotype DX assay. Exact P-values were calculated. The proportion of physicians who were more confident in their treatment recommendations following use of the assay was calculated.

RESULTS

Patients and Tumor Characteristics

One hundred consecutive women diagnosed with early stage (I–IIIa) ER-positive breast cancer with 0–3 positive lymph nodes were invited to participate in the study. Of these, two patients were ineligible to participate because of inadequate samples (one tumor sample did not have sufficient invasive tumor and one sample did not meet testing criteria) and two patients did not have completed questionnaires, bringing the evaluable cohort to 96 patients (Table I). The majority of the patients (n = 62; 65%) were lymph node-negative (N0), 1 (1%) had micrometastatic (N1mic) disease, and 33 (34%) had 1–3 node-positive lymph nodes; yielding a cohort of 34 N+ patients (35% of the evaluable population). The tumor grade distributions were: 24 (25%) Grade I, 47 (49%) Grade II, and 25 (26%) Grade III. The mean tumor diameter was 2.3 cm (median = 2.0, range = 0.5–9.0). ER by RT-PCR ranged from 5.8 to 12.5 (≥6.5 positive), PR by RT-PCR ranged from 3.2 to 13.2 (≥5.5 positive), and HER2 by RT-PCR ranged from 7.6 to 11.2 (<10.7 negative, 10.7 to <11.5 equivocal, ≥11.5 positive).

In this cohort 46 (48%) results were categorized as Low risk (<18), 30 (31%) were Intermediate risk (18–30), and 20 (21%) had High risk (≥31) results (Table II). A sizable proportion of both N0 and N+ patients were classified as Low risk. Of the 62 N0 patients, 28 (45%) were categorized as Low risk, 20 (32%) were categorized as Intermediate, and 14 (23%) were categorized as High. Of the 34 N+ patients, 18 (53%) results were categorized as Low, 10 (29%) were categorized as Intermediate, and 6 (18%) were categorized as High.

| Total number of cases | N (%) |
|-----------------------|-------|
| Total number of cases | 96 (100%) |

| Patient Age (years) | N (%) |
|---------------------|-------|
| 32–39 | 6 (6%) |
| 40–49 | 23 (24%) |
| 50–59 | 26 (27%) |
| 60–69 | 28 (29%) |
| 70–79 | 11 (11%) |
| 80–89 | 2 (2%) |

| Tumor diameter (cm) | N (%) |
|---------------------|-------|
| ≤1 | 12 (13%) |
| >1–2 | 41 (43%) |
| ≥2–4 | 36 (38%) |
| >4 | 7 (7%) |

| Tumor grade | N (%) |
|-------------|-------|
| Grade I | 24 (25%) |
| Grade II | 47 (49%) |
| Grade III | 25 (26%) |

| T stage | N (%) |
|---------|-------|
| 1 | 54 (56%) |
| 2 | 39 (41%) |
| 3 | 3 (3%) |

| N stage | N (%) |
|---------|-------|
| N0 | 62 (65%) |
| N+ | 34 (35%) |

| N1mic | 1 (1%) |
| 1–3 positive nodes | 33 (34%) |

N0, node-negative; N+, node-positive.
Impact on Treatment Recommendations

For the entire cohort of 96 patients, 50 (52%) initially received a recommendation for HT alone and 46 (48%) received an initial recommendation for CHT; none received a recommendation for CT without HT (Table IIIa). A total of 31 of 96 patients (32%; 95% CI 23–43%) had a change in treatment recommendations following receipt of the assay results and re-evaluation by the multidisciplinary committee. In the N0 cohort, 17 of 62 patients (27%, 95% CI 17–40%) had a change in treatment recommendations (Table IIIa); among the 34 N+ patients, 14 (41%, 95% CI 25–59%) had a change in treatment recommendation (Table IIIb).

Impact on Recommendations for Chemotherapy-Based Regimens

Following receipt of the Oncotype DX results, the proportion of patients receiving a recommendation for chemotherapy-based regimens decreased from 48% to 34% post-assay (P = 0.024, McNemar’s test) (Table IVa).

The proportion of the 62 N0 patients receiving a recommendation for a chemotherapy-based regimen was 42% pre-assay and 35% post-assay (Table IVb). This change was not statistically significant (P = 0.45, McNemar’s test). The number of patients that initially received a recommendation for HT alone that was changed to include chemotherapy post-assay was 6 (10%) of N0 patients.

Of the 34 N+ patients, 14 (41%) initially received a recommendation for HT alone and 20 (59%) initially received a recommendation for CHT (Table IVc). Following receipt of the assay results, the proportion of patients who received a recommendation for a chemotherapy-based regimen decreased from 59% to 32% (P = 0.023 for McNemar’s test).

Of the 10 N0 patients whose recommendations changed from CHT to HT, 7 (70%) had low Recurrence Score results and 3 (30%) had scores within the lower portion of the intermediate range. Of these 10 patients, 9 had tumor sizes of at least 2.0 cm and 7 were under age 50. On the other hand, of those recommended changes from HT alone to CHT or CT, 2/6 (33%) had high Recurrence Score results and the remaining 4/6 (67%) had scores within the higher portion of the intermediate range. Three of these patients had grade 1 tumors, one had a tumor under 1.0 cm, and all were over age 50.

A similar proportion of the N+ patients who had a change in treatment recommendation from CHT to HT alone (7/11, 64%) had Recurrence Scores results in the Low range. The remaining 4/11 (36%) had Recurrence Score results in the low end of the Intermediate range. Both N+ patients who received a CHT treatment recommendation in lieu of HT had Recurrence Score results in the Intermediate range.

During the course of the study, the tumors from three patients were determined to have a triple negative phenotype (ER−, PR−, and HER2−) by RT-PCR, although initially they had been classified by immunohistochemistry as ER+. All three had their treatment recommendations changed to CT alone.

Physician Confidence in Treatment Recommendations

Following documentation of the post-assay treatment recommendation, the attending physicians were asked if they were more confident in the treatment recommendations. Of the 96 responses, 63 (66%) strongly agreed with this statement, 25 (26%) agreed, and 8 (8%) neither agreed nor disagreed. There were no physicians who either disagreed or strongly disagreed with the statement. Overall, physicians agreed or strongly agreed that they were more confident in the treatment recommendation after incorporating the Oncotype DX assay results in 88 of 96 cases (92%, 95% CI 84–96%).

DISCUSSION

This prospective decision impact study of the 21-gene breast cancer assay is the largest to date in Latin America and the first such study within the Mexican public health care system.

Overall, treatment decisions changed for 32% of patients with the use of the Oncotype DX assay, with 13 fewer patients receiving a change regarding their initial recommendation for adjuvant chemotherapy after consideration of the assay results. When analyzed by nodal status, treatment decisions changed for 27% of N0 patients and 41% of N+ patients. Fewer N0 patients (6% of N0 patients) and 9 fewer N+ patients (26% of N+ patients) received recommendations for adjuvant chemotherapy after assay results were considered. The impact on

TABLE II. Recurrence Score Results by Nodal Status

| Recurrence Score group | N0 (N) | N+ (N) | Total (N) |
|------------------------|--------|--------|-----------|
| Low (<18)              | 28 (45%) | 18 (53%) | 46 (48%)  |
| Intermediate (18-30)   | 20 (32%) | 10 (29%) | 30 (31%)  |
| High (≥31)             | 14 (23%) | 6 (18%)  | 20 (21%)  |
| Total                  | 62      | 34      | 96        |

N0, node-negative; N+, node-positive.

Impact of the 21-Gene Breast Cancer Assay

This table shows the changes in recommendations for chemotherapy for different groups of patients based on their breast cancer status.

TABLE IV. Changes in Recommendations for Chemotherapy

|            | Pre-Oncotype DX | Post-Oncotype DX |
|------------|-----------------|------------------|
| HT (N %)   | CHT (N %)       | CT (N %)         | Total (N %)     |
| All patients |                 |                  |                |
| HT          | 42 (44)         | 7 (7)            | 1 (1)          | 50 (52)       |
| CHT         | 21 (22)         | 23 (24)          | 2 (2)          | 46 (48)       |
| Total       | 63 (66)         | 30 (31)          | 3 (3)          | 96 (100)      |
| Node-negative patients |          |                  |                |
| HT          | 30 (48)         | 5 (8)            | 2 (2)          | 36 (58)       |
| CHT         | 10 (16)         | 15 (24)          | 2 (2)          | 26 (42)       |
| Total       | 40 (65)         | 20 (32)          | 2 (3)          | 62 (100)      |
| Node-positive patients |          |                  |                |
| HT          | 12 (35)         | 2 (6)            | 0 (0)          | 14 (41)       |
| CHT         | 11 (32)         | 8 (24)           | 1 (3)          | 20 (59)       |
| Total       | 23 (68)         | 10 (29)          | 1 (3)          | 34 (100)      |

HT, hormonal therapy; CHT, chemohormonal therapy; CT, chemotherapy.
treatment decision-making within the node-positive population supports the clinical utility of the Oncotype DX assay within this group.

There was a lower proportion of CHT recommendations at baseline than had been previously reported in the literature for this Mexican patient demographic [4,5]. In this study, 48% of patients (42% of N0 and 59% of N+ patients) received an initial recommendation for CT or CHT. Had the proportion of recommendations for CT/CHT been similar to previous reports (60–90% for early stage, hormone-positive, HER2-negative patients seen in the Public Health System [3,6,7]), it is possible that a higher proportion of changes from CHT to HT might have been observed. The patients in this study were not selected by physicians for inclusion, thus reducing the likelihood that selection bias accounts for this result. However, initial recommendations may have been impacted by the knowledge that patients were study participants. Also, the recommendations were determined by a committee versus an individual practitioner, which could have had an effect on the initial treatment recommendation.

The application of Recurrence Score information by the multidisciplinary committee is consistent with previous studies in other countries [14–21]. Two-thirds of the Recurrence Score results were Low category and the rest were classified as Intermediate in the group of patients who were switched from a CHT treatment recommendation to an HT treatment recommendation post-Oncotype DX assay. In the patients that were switched from HT to CHT there were no Low Recurrence Score results, 75% Intermediate, and 25% High results. This result supports the conclusion that Recurrence Score information was used to arrive at a treatment decision in this setting.

The majority (92%) of physicians felt more confident in their treatment recommendation after receiving the Oncotype DX results. This suggests a level of comfort in integrating the multi-gene assay information with clinicopathologic variables in determining treatment recommendations. This confidence indicates assay value in clinical practice, since physicians felt that their treatment recommendations, both those changed and those confirmed, were more informed by utilizing the Oncotype DX assay.

These results demonstrate that the Recurrence Score result was used to allocate chemotherapy to those with the highest anticipated benefit and to spare those with minimal if any expected benefit: treatment recommendation changes occurred both towards and away from chemotherapy. There was a net decrease in chemotherapy recommendations, and by reducing adjuvant chemotherapy usage, the cost of treatment within this patient population may decrease. A modeling study of the cost-effectiveness analysis of the assay in Mexico showed that use of the test decreased chemotherapy use in 46% of eligible patients, which led to a cost savings of MXN 27,414 per patient [29]. Health economic studies on use of the Oncotype DX assay in the Mexican public healthcare system to manage patients with early stage, ER-positive breast cancer are needed to understand the assay’s financial value in Mexico’s health care system.

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