Use of the Oncotype DX® test for therapeutic decision-making in the context of treating invasive breast cancer

English summary

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This is the English summary of the guidance entitled Utilisation du test Oncotype DX^{MD} aux fins de décision thérapeutique dans le contexte du traitement du cancer du sein infiltrant published in March 2016.

The complete version of this guidance (in French) is available on the website of INESSS in the *Publications* section.

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SUMMARY

Introduction

Approximately 6 000 new cases of breast cancer are diagnosed in Québec each year, most of which are hormone-dependent. To treat this type of cancer, hormonal therapy (HT) is generally prescribed after surgery to reduce the risk of recurrence, sometimes with adjuvant chemotherapy (CT) when the benefit of adding it is considered to outweigh the risks involved. The Oncotype DX® (ODX) gene expression test, which came on the market in 2004, joined the available tools for helping clinicians in this therapeutic decision-making. The test, which is performed on a tumour sample, measures the expression of 21 genes, and the result, expressed as a Recurrence Score® (RS) between 0 and 100, indicates the patient's individual risk, that is, the probability that she will experience a distant recurrence during the 10 years following surgery.

The ODX test, which is performed only in the manufacturer's laboratory in the United States, is covered by the Régie de l'assurance maladie du Québec (RAMQ) in certain conditions defined in terms of reference drafted by the Direction générale de cancérologie (DGC). Given the high cost of this test and questions raised about its value-added in the literature, the DGC asked INESSS to assess the test's clinical utility and value-added and to then update the terms of reference for its use.

Methods

This report stems from an exhaustive review of the literature on the clinical validity and utility of the ODX test in the context of treating early-stage invasive breast cancer and on its value-added in relation to other prognostic tools, such as the standard clinicopathological parameters (CPPs), the Ki67 marker, Magee equations, Adjuvant! Online (AOL) and the Nottingham Prognostic Index (NPI). Its analytical validity was examined as well. The scientific literature published up to the end of June 2015 was considered, although a literature watch was conducted up to early December 2015. A single evaluator selected and mined the scientific data. An ad hoc advisory committee consisting of medical and surgical oncologists, epidemiologists and an anatomical pathologist was formed to evaluate the evidence and develop suggestion for updating the terms of reference for the use of the ODX test.

Results

Analytical validity

The analytical validity evidence for the ODX test is based on a small number of studies conducted by the manufacturer on a small number of samples. These studies found the test to be reliable (intra-laboratory repeatability and reproducibility) (standard deviation 3 $\leq$ RS units). Inter-laboratory reproducibility was, on the other hand, not assessed, given that the test could not be performed in any laboratory other than that designated by the manufacturer. No external quality control was presented.

Clinical validity

To date, two retrospective studies involving samples archived in randomized clinical trials (RCTs) and that were not specifically intended for the purpose of studying the ODX test (NSABP-B-14 and ATAC) reported that it has significant prognostic value in patients with early-stage, node-

negative, estrogen receptor-positive (ER+) invasive breast cancer. Most of these patients were treated with tamoxifen. In one of the studies, certain postmenopausal patients were treated with anastrozole.

Furthermore, two retrospective studies involving samples archived in RCTs and that were not specifically intended for the purpose of studying the ODX test (SWOG-8814 and ATAC) showed that it has significant prognostic value in postmenopausal patients with node-positive, ER+ invasive breast cancer. However, this prognostic ability might be limited to the first five years of follow-up.

Overall, the assigned level of evidence for the clinical validity of the ODX test is low because of the retrospective study designs, but large RCTs are presently underway and may, if the results are conclusive, increase the level of evidence

Clinical utility

No study measuring the direct impact of using the ODX test on patient's long-term clinical outcomes (improvement in survival, decrease in complications, etc.) was identified. There is, however, average-quality indirect evidence of the test's clinical utility. It seems to be able to identify patients in whom CT will confer a significant benefit and others in whom it will not confer any benefit, and to modify treatment recommendations and reduce by approximately 11 % the recommendation to use CT in patients with stage N0 breast cancer (the results concerning patients with stage N1 are highly variable). In addition, the test can probably improve the clinician's confidence in his/her treatment recommendation and reduce the decisional conflict experienced by some patients.

Potential role of other prognostic tools

According to the available data, when used alone, none of the other prognostic tools evaluated (the Ki67 marker, Magee equations, AOL or NPI) is fully equivalent to the ODX test. In other words, there is always certain discordance between the risk categories defined by the two tools. However, the ODX test score can be predicted relatively easily by combining several standard CPPs, namely, the histological grade, the nuclear grade, the mitotic index and the level of hormone receptor (HR) expression. In fact, it seems fairly rare for an ODX test performed on a tumour with a seemingly good prognosis based on standard CPPs (a low histological grade and strong HR expression or a low proliferation index) to show a high RS. Prognostic tools such as the Ki67 marker and Magee equations may help better select patients requiring an ODX test, for example, by ruling out the possibility that a patient will obtain a low or high RS that could result in the reversal of an initial treatment decision. Local validation of these tools in the context of a prospective study would, however, be necessary.

Economic studies

The Canadian economic studies conclude that the ODX test has a good cost-effectiveness ratio (in terms of quality-adjusted life-years, or QALY), its differential cost-effectiveness ratios (ICERs) varying according to the different analyses. The results of the sensitivity analyses show a very highly variable probability (54 to 100 %, depending on the model) of obtaining a cost-effectiveness ratio below the cutoff point of CAD$50,000 or CAD$100,000.

Conclusions

The ODX test is a prognostic and predictive tool of the benefit of adding adjuvant CT to treatment in patients with early-stage, HER2-/ER+ breast cancer treated with HT. The level of evidence for the test's predictive value is, however, low because of the methodological limitations of the available studies. Nonetheless, it seems that this tool facilitates decision-making regarding the need to recommend adjuvant CT in node-negative patients by modifying the treatment recommendation in about 30 % of the cases and reducing by about 11 % the recommendation to use CT. However, a better histopathological evaluation of the tumour subtype could diminish this effect of the ODX test. Furthermore, there is presently no evidence indicating that treatment decision changes (withdrawing or adding CT) based on the result of the ODX test improves patient's long-term outcomes, in particular, recurrence-free survival.

Since there is no alternative that is fully equivalent to the ODX test, INESSS considers that this test has value-added in certain circumstances where clinical decision-making is difficult. However, the result of an ODX test should always be considered together with all the other standard CPPs and never replace the clinician's judgment, especially because of the weakness of the evidence for its predictive value. Consequently, it is important that the test be ordered only after the appropriateness and feasibility of CT have been thought through by a clinician who has a good understanding of the molecular subtypes of breast cancer. Furthermore, to promote the judicious use of the test, the patient should participate in this deliberation that leads to the test being ordered.

Although INESSS considers that the ODX test has a role to play as a clinical decision-making tool in certain breast cancer cases, it feels that its use (ordering and the approval process) needs to be monitored, especially because of its high cost and because it's value-added is probably limited in certain clinical circumstances. Consequently, INESSS proposes a standardized ODX test requisition form, to which the anatomical pathology report should be attached for perusal. The data gathered on the characteristics of all the patients in whom the test is ordered and the results of these tests could then be analyzed, after which a review of the eligibility criteria or an optimal usage guide could be proposed, if necessary.

Regarding the updating of the terms of reference for the use of the ODX test, INESSS, after consulting an expert panel, advice that the Direction générale de cancérologie (DGC):

- maintain the coverage of the ODX test granted to patients with newly diagnosed HER2-/ ER+ invasive breast cancer with no lymph node involvement or with microinvasion (stage N1mi) who present with or whose tumour presents with one of the following characteristics:
  - Stage pT1b (> 0.5 cm to 1.0 cm) and:
    - A histological grade of 2 and weak HR expression (ERs < 80% or PRs < 20%),
    - A histological grade of 2 and young age (≤ 40 years),
    - A nuclear or histological grade of 3, or
    - A high proliferation index;
  - Stage pT1c (> 1.0 to 2.0 cm) and:
    - Grade 1 and weak HR expression (ERs < 80% or PRs < 20%),
    - Grade 1 and young age (≤ 40 years),
    - Grade 1 and a high proliferation index, or
    - A histological grade of 2 or 3;

- Stage pT2 (> 2.0 cm to 5.0 cm) and:
  - A histological grade of 1 or 2, or
  - A histological grade of 3 and PRs ≥ 20%;
- make the following ineligible for the test:
  - Postmenopausal women with classical lobular carcinoma with no unfavourable factors,
  - Patients with adenoid cystic or tubular carcinoma,
  - Patients over the age of 80 years, and
  - Patients who will not receive adjuvant HT (tamoxifen or AIs).

INESSS also suggest:

- Monitoring the use of the ODX test and ODX test results and creating a mechanism for monitoring adherence to the eligibility criteria;
- Creating a standardized ODX test requisition form (see the end of this notice);
- Issuing a directive stating that the test must be ordered by the clinician who will make the decision to initiate or not initiate CT;
- Strengthening the directive stating that the patient must be consulted about the option of using adjuvant CT before the ODX test is ordered.