INAHTA Briefs

Issue 2008/096

Diagnostic Performance of Techniques Used for HER-2 Testing in Breast Cancer

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Reference 2008-03. ISBN 978-2-550-52721-3.
www.aetmis.gouv.qc.ca/site/fr_publications_2008.phtml

Aim

To comparatively assess methods for determining the HER-2 status of breast cancer patients for the purpose of evaluating their eligibility for trastuzumab therapy.

Conclusions and results

The conclusions and recommendations may serve as a basis for developing clinical practice guidelines for testing and for the Ministry of Health and Social Services to organize services provided by pathology laboratories.

This assessment shows that when immunohistochemistry (IHC) is used as the initial diagnostic test, as is generally the case in Québec, nearly three-fourths (~73%) of breast cancer patients test negative (a score of 0 or 1+). The vast majority (97.4%) of negative IHC results can be confirmed by fluorescence *in situ* hybridization (FISH). As for patients who test positive on IHC (a score of 3+), only 89.9% test positive on FISH. IHC requires a high level of expertise. The level of agreement among pathologists in interpreting test results varies considerably from study to study. Moreover, concordance between IHC and FISH results is better when the tests are performed at central laboratories as opposed to local laboratories. Regarding local laboratories, there are reports of high proportions of positive IHC results (18.4% to 36.4%) that subsequently turned out to be negative when the cases were retested at a central or reference laboratory. Furthermore, chromogenic (CISH) and silver-enhanced (SISH) in situ hybridization tests are not always equivalent, in terms of accuracy, to FISH. The diagnostic performance of CISH is very good, but only when the HER-2 and CEP17 probes are used in a complementary manner. Published results on the performance of SISH are scarce, and the sensitivity of this test appears to be low (~82%). No evidence supports real-time PCR or reverse transcriptase PCR as alternatives to FISH in a clinical setting, as they have difficulty detecting FISH-positive cases. These findings, together with the fact that the caseload is insufficient in some laboratories in Québec and that the testing algorithms vary, support the absolute necessity of internal and external laboratory quality assurance and the need for more centralized testing.

Recommendations

AETMIS recommends: (1) that the authorities implement an HER-2 testing quality assurance program in Québec and designate at least one reference laboratory; (2) that laboratories follow the Canadian recommendations on the use of IHC and FISH tests, in particular the use of IHC initially, followed by FISH (or other validated in situ hybridization tests) in cases of equivocal results; (3) that FISH be the initial test performed when the quality of the sample received by the laboratory is questionable; and (4) that CISH be performed with two probes to confirm an equivocal IHC result, one for the HER-2 gene, the other for the chromosome 17 centromere.

Methods

We systematically reviewed the literature on the diagnostic performance of IHC, CISH, SISH, and real-time PCR and RT-PCR in breast cancer. FISH is used as the gold standard. Interobserver agreement and interlaboratory reproductibility are also assessed. This report includes an analysis of studies published from January 2000 through November 2007.

Further research/reviews required

The diagnostic performance of silver-enhanced in situ hybridization should be the subject of a literature watch until the evidence confirms the validity of this technique.

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ISSN 1654-501X