Medical Xpress

Biomarker tests in breast cancer: Decision on chemotherapy remains difficult

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The German Institute for Quality and Efficiency in Health Care (IQWiG) investigated the benefit of biomarker tests to support the decision for or against adjuvant systemic chemotherapy in certain breast cancer patients, that is, women with primary hormone receptor-positive, HER2-negative breast cancer and up to 3 affected lymph nodes.

When the Institute presented its preliminary report in November 2015, the evidence was inadequate to prove the benefit or harm of such tests. However, the results of further relevant studies had been announced for the beginning of 2016. Following a request by the Federal Joint Committee (G-BA), IQWiG did not immediately start preparing the final report after the scientific debate on the preliminary report, but waited for these results.

In the summer of 2016 the first results of one of these studies (MINDACT) were published; these results could be considered in the final report and are now the focus of discussion. The new study data provide valuable information on the potential consequences of omitting chemotherapy on the basis of a biomarker test result.

However, one cannot speak of a clear benefit of the test investigated in the MINDACT study. This is because, on the one hand, the follow-up period of 5 years is too short; many cases of distant metastasis, that is, metastasis not in the vicinity of the affected breast, occur only after several years. On the other, it is questionable whether 1 to 2% more deaths caused by the recurrence and spreading of the cancer due to the omission of chemotherapy are really negligible.

Biomarkers aim to show who benefits from chemotherapy

IQWiG investigated the benefit of the use of biomarkers to support the treatment decision of women for whom it is so far unclear whether they would experience a recurrence of disease at all or whether their cancer would respond to chemotherapy. If this were not the case, chemotherapy would be an unnecessary burden. This question is open in patients with primary hormone receptor-positive, HER2-negative breast cancer with at most 3 affected lymph nodes. Chemotherapy after successful tumour surgery aims to eliminate potential micrometastisis and thus prevent disease recurrence. However, even without chemotherapy, most women affected do not experience a recurrence. The group of patients who actually benefit from chemotherapy cannot be reliably determined solely on the basis of established factors such as age, lymph node status, and grading. The hope is that so-called biomarkers can provide reliable conclusions on the benefit of such adjunctive therapy.

Many study results could not be considered

The literature analysis identified 8 studies that were relevant for the research question of the benefit assessment. In 6 of these studies, the data of many patients were missing, for example, because samples had already been used for other analyses, were not suitable for the test or no consent had been given for the renewed use of the sample. If the evidence base is so incomplete, in particular for the important long-term analyses, then this can lead to biased conclusions. The results of these studies could therefore not be used for the benefit assessment.

A further study investigated the decision on the choice between 2 chemotherapies, but not the potential omission of chemotherapy. The following text therefore refers solely to the 8th study, MINDACT.

Almost every second woman with a high clinical risk score has a favourable biomarker test result

The MINDACT study, a randomized controlled trial, included nearly 7000 women with early-stage breast cancer who had undergone surgery. Most study participants fulfilled the inclusion criteria for the present assessment.

The participants underwent both a conventional clinical risk assessment and a genomic risk assessment to estimate the risk of distant metastasis (classified as "low" or "high" in both assessments); if distant metastasis occurs, 2 out of 3 women affected die of cancer within 10 years. The clinical risk assessment yielded a low score in half of the women analysed; the score was high in the other half. In the genomic risk assessment, the tumour samples were tested with a biomarker (MammaPrint), which determines the expression of 70 genes (gene expression profile). In 46% of the women with a high clinical risk score, the additional application of this test yielded a low genomic risk score. Half of these women received chemotherapy to determine whether women with such a discordant risk assessment would benefit from chemotherapy.

5-year results only allow cautious estimation

In the commenting procedure on IQWiG's preliminary report, the participating experts agreed that distant metastasis and other complications of breast cancer could occur many years after the primary tumour, so a follow-up period of at least 10 years needs to be considered. However, the recently published first results of the

MINDACT study cover only a 5-year period. For this reason, no reliable assessment is so far possible of the advantages or disadvantages of omitting chemotherapy on the basis of low biomarker risk scores. IQWiG could only roughly estimate the results to be expected after 10 years.

Stefan Lange, IQWiG's Deputy Director notes: "No one knows exactly whether the differences between the groups with and without chemotherapy will increase or decrease in the next years or whether the rate of distant metastasis will be similar. But the results now available are the best we can currently work with. It is a good thing that this large and carefully planned study was conducted. Of the approximately 70,000 women diagnosed with breast cancer in Germany every year, it is unclear for a roughly estimated number of 20,000 whether they will benefit from chemotherapy. The MINDACT study provides important data for these women and their physicians in order to be able to discuss in detail the advantages and disadvantages of chemotherapy and the limited informative value of biomarker tests."

Hurdle narrowly taken - or knocked over after all?

The study authors sought primarily to evaluate whether a treatment decision based on the biomarker test result is inferior to a treatment decision based on the clinical risk score. For this purpose, they defined (in advance and with statistical specifications) that in women with a high clinical and low genomic risk score who omitted chemotherapy, the 5-year survival rate without distant metastasis ("distant metastasis-free survival") would have to be at least 92%. This was actually the case in 94.7% of the women; the corresponding 95% confidence interval was 92.5% to 96.2%. The crucial lower boundary of this interval is just above the defined threshold of 92%; according to the study authors, this demonstrates non-inferiority.

However, this is an unconventional understanding of non-inferiority: Instead of evaluating only one study arm, the risk of distant metastasis of women in the groups with and without chemotherapy should have been compared. In addition, the 5-year threshold of 92% was not explained, in contrast to the one specified by IQWiG, namely, a 10-year rate of distant metastasis-free survival of 95%. This threshold has already been undercut. Other experts define a more liberal threshold of 90%. This criterion will probably not be fulfilled either: As, according to experts, many recurrences occur only years later, the lower boundary of the confidence interval will probably drop under 90% in the next 5 years.

A difference of 1.5% - or even 4%?

Besides, for the commission awarded to IQWiG by the G-BA, other results of this study are more important. If women with a high clinical and low genomic risk score receive or omit chemotherapy, how large is the 5-year difference between groups with regard to the rates of local or distant recurrence, and, in particular, deaths? The study authors determined that, after 5 years, 95.9% of women who had undergone chemotherapy were free of distant metastasis; in women who had not, this rate was 94.4%, a statistically non-significant difference of 1.5%. However, because of the uncertainty caused by the limited number of participants, this difference could also amount to nearly 4%.

But for women affected, disease-free (i.e. recurrence-free) survival and overall survival are at least as important as distant metastasis-free survival. In the study, the treatment effects were in the same direction for all 3 outcomes.

If 1000 women omit chemotherapy on the basis of a low biomarker score, then 32 additional recurrences of any type (including deaths) can be expected; but due to uncertainty, this number could increase to 61. Regarding mortality alone, 11 additional deaths can be expected; this number could increase to 26.

How many deaths due to omission of chemotherapy are negligible?

Stefan Lange notes: "According to the study authors, the difference between groups is so small that many women with breast cancer might not require chemotherapy. I would like to discuss that in more detail with the women affected and with experts. In other discussions, for example, on the introduction of colorectal or prostate cancer screening, alleged increases in survival rates of a fraction of a percent have been propagated as essential goals to be aspired. But in the case of the decision on chemotherapy, it is supposed to be negligible that of the approximately 10,000 women per year who, according to the manufacturer information, could omit chemotherapy thanks to the new test, up to 260 more could die?"

How does one balance chemotherapy-related harm against cancer-related harm?

This would be comprehensible if the higher risk were accompanied by very clear advantages. A breast cancer patient with a high risk of distant metastasis according to the clinical assessment but a low risk according to the genomic assessment must on the one hand consider the potential side effects and late complications of chemotherapy and on the other, the higher risk of future distant metastasis or cancer-related death.

Daniel Fleer, the responsible project manager from IQWiG's department of Non-Drug Interventions, explains: "Unfortunately, most statements on the disadvantages of chemotherapy are rather vague. It is repeatedly stated that an estimated 2 to 3% of patients undergoing chemotherapy suffer serious harm, for instance, permanent damage to internal organs such as the heart of kidney, or even die. However, these are only very rough estimates that are simply cited, often without any supporting evidence. Thanks to the MINDACT study, women affected now have substantially more information on the extent of the risk of omitting chemotherapy. However, no information has been provided so far on side effects that are important for decision-making. For the time being, 1 of the 2 components required to make an informed decision thus remains unclear. Overall, IQWIG concludes that the data on the currently available biomarkers provide no hint of a benefit or harm of a biomarker-based strategy to support the decision for or against adjuvant chemotherapy in primary breast cancer. At the moment one cannot in good faith advise a woman with a high clinical risk and low genomic risk to omit chemotherapy. The actual "added value" of the biomarker test for women affected can only be judged when further results of ongoing studies become available.

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