Reducing cardiac monitoring during HER2-directed treatment

The Dutch NVMO Committee for Sustainability and Efficiency has formulated recommendations to reduce the frequency of cardiac monitoring during HER2-directed therapy. The goal is to reduce time and radiation burden for the patient and reduce unnecessary use of resources and environmental impact without increasing the risk of undetected loss of cardiac function.

Introduction

Patients with an HER2-positive metastatic malignancy are eligible for systemic treatment with anti-HER2 therapy, primarily trastuzumab. Anti-HER2 targeted therapy has led to a significant and meaningful survival benefit in patients, especially in patients with breast cancer. (1) The median overall survival of these patients currently exceeds 5 years. (2) A significant side effect of trastuzumab treatment is a decrease in left ventricular ejection fraction (LVEF). This is usually reversible and is mainly observed in the setting of concurrent or recent treatment with anthracyclines or in the case of known cardiovascular morbidity. (1,3)

National and international guidelines recommend monitoring the LVEF using multigated radionucliede angiograpy (MUGA) or echocardiography every three months during trastuzumab treatment. (5-8, 15,16) The costs of these examinations are approximately 340 and 205 euro's, respectively, in the Netherlands. In clinical practice, symptomatic heart failure and/or clinically relevant decrease in ejection fraction are rare, especially without recent anthracycline treatment, such as during prolonged treatment in the metastatic setting.

Question

Can routine determination (every three months) of the LVEF be safely omitted in patients with HER2-positive metastatic breast cancer who are treated with trastuzumab or a trastuzumab-antibody drug conjugate?

Objective

To reduce the number of investigations to determine the LVEF, thereby reducing healthcare consumption, reducing environmental impact, saving costs, and saving time for the patient. Additionally, omitting MUGA scans has a positive impact on reducing the demand for scarce nucleotides and reducing their environmental burden.

Literature summary

In a meta-analysis of individual patient data from three landmark trials with trastuzumab in the adjuvant setting, the incidence of trastuzumab-related cardiotoxicity was 11%, primarily involving asymptomatic mild decreases in LVEF (9%) (3). Risk factors for a decline in LVEF included baseline LVEF < 60%, Body Mass Index >25, age > 60 years, and hypertension.

Concurrent or recent anthracycline treatment and prior radiotherapy also increased the risk of trastuzumab-related cardiotoxicity. (8)

The cardiotoxicity of trastuzumab is often reversible with conservative measures (3), and in 62-88% of patients with a decline in their LVEF, trastuzumab can be re-administered after a break without further deterioration of the LVEF (9,10,11) There is no data showing that early intervention prevents symptomatic heart failure. (13) Further research is ongoing. (12,14)

A Dutch cohort study in patients with HER2-positive metastatic disease showed that the incidence of LVEF decline is highest in the first two years of treatment. (10) This study also identified risk factors for LVEF decline, largely consistent with the meta-analysis in the adjuvant setting (baseline LVEF < 60%, previous cardiac complaints/symptoms, smoking). Based on this, the authors considered that cardiac monitoring during prolonged trastuzumab use can be omitted in non-smoking patients without cardiotoxicity during previous adjuvant trastuzumab therapy and a baseline LVEF ≥60%. Moreover, in a large proportion of patients with reduced ejection fraction, trastuzumab treatment could be safely continued (10,11). Another Dutch cohort study showed that in patients with a reduced LVEF (40-50%) before starting antiHER2 treatment, severe cardiotoxicity (defined as a decrease in LVEF to <40%) occurred in 35% and was largely reversible with cardioprotective medication. (11)

Current guidelines allow for significant individualization of cardiac monitoring for patients treated with trastuzumab in the metastatic setting. According to the Dutch guideline, anti-HER2 treatment can be continued as long as it is acceptable in terms of toxicity. Whether cardiac toxicity should be determined clinically or through evaluation of the LVEF is not specified. (4) The ESMO guideline recommends evaluating cardiac toxicity by physical examination, biomarkers, and/or imaging. The frequency of evaluation is not specified, and continuation of HER2-direcrted therapy in case of reduced LVEF is considered an option in asymptomatic patients. (5) The UK-NCRI recommends monitoring during the first eight months and subsequently as assessed by the physician in consultation with the patient. The method of monitoring is not specified. (6) Finally, the ASCO guideline indicates that there is little evidence for a recommendation. Echocardiography can be considered. Patient characteristics and clinical assessment determine whether and how often examinations should take place. (7)

Recommendation

Routine monitoring of LVEF in patients with HER2+ metastatic breast cancer during treatment with trastuzumab or trastuzumab-ADC is not indicated based on the low incidence of clinically relevant cardiac toxicity and its reversibility after discontinuation of treatment. The significant contribution of trastuzumab to the effectiveness of treatment plays an important role in this.

In patients with one or more risk factors (smoking, baseline LVEF <60%, cardiotoxicity during previous adjuvant treatment), consideration may be given to monitoring LVEF every three months during the first two years of treatment.

With a median OS of 5 years, this would result in a saving of 20 investigations per patient in the Netherlands. Annually, based on a Dutch prevalence of 600 patients with HER2-positive

metastatic disease, this would save approximately 2400 investigations and 500,000-800,000 euro's.

About the Authors:

The committee "sustainability and efficiency" of the Dutch Society of Medical Oncology (NVMO) was initiated in 2022. Their remit is to demonstrate that it is possible to increase both the sustainability as well as the efficiency of medical oncology care. The committee consists of medical oncologists and hospital pharmacists. They regularly publish specific guidelines and suggestions for daily practice based on both published literature and daily experience. All published guidelines are freely accessible at "https:www.nvmo.org/duurzaam-en-doelmatigheid/".

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