Serial Monitoring of Serum HER-2 Extra-Cellular Domain during Herceptin®-Taxotere® or Herceptin®-alone Therapy for Metastatic Breast Cancer Patients: Preliminary Results from the French Experience (HER.M.E.S protocol).

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Rationale

HER2 over expression is a prognostic factor. It is also the target of trastuzumab (anti HER2 monoclonal antibody immunotherapy). In approximately 60% of Metastatic Breast Cancer (MBC) patients with HER2 over-expressed tumours, the HER2 extra cellular domain (H-ECD), undergoes proteolytic cleavage from the full-length protein and is shed as a circulating "antigen". H-ECD could be detected by enzyme immunoassay.

Trastuzumab therapy had to be probably early initiated in MBC patients over expressing HER2. Different protocols are possible (trastuzumab alone or with chemotherapy). Two modalities of trastuzumab treatment are possible in France: monotherapy for patients pre-treated with anthracyclines and taxanes; or associated with paclitaxel for patients pre-treated by anthracyclines.

French ministry of health, searching to evaluate the economical impact of trastuzumab treatment in MBC has mandated a multicentric group for answering this question.

H-ECD has been also reported to be a treatment efficacy independent predictor, but essentially regarding the initial level at MBC. The serum H-ECD kinetic, (level ratio before treatment/after one cycle) is not used routinely as an early predictor of trastuzumab and/or chemotherapy sensitivity.

In this prospective trial we try to evaluate the potential impact of serum H-ECD kinetic on clinical monitoring of HER2+ MBC receiving trastuzumab therapy.

Material and Methods

French protocol HER.M.E.S is a phase IV multicentric study, evaluating the pharmaco-economic aspect of trastuzumab treatment on MBC with HER2 overexpressing tumours. We were also interested to determine whether serum levels of H-ECD would predict the course of disease in HER2+ MBC patients. Patients in first or second line MBC untreated with trastuzumab were first precluded to determine HER2 status. Only HER2 positive patients were finally included. Trastuzumab was delivered weekly (2mg/kg) or three weekly (6mg/kg) associated or not with paclitaxel (175 mg/m² weekly or 80 mg/m² weekly). Treatment were delivered until progression or unacceptable toxicity.

HER2 tumour status was determined using Immunohistochemistry methods (IHC) or FISH (+ > 2 genes copies per nucleus). H-ECD status was determined using a centralised elisa technique (Oncocepte Science-Bayer Diagnostic®). (Elsa kit). The H-ECD levels were determined during the following periodic: pre-inclusion (day 0), then days 28, 36, 64, 102 and 120 for HER2+ patients.

Evaluation of the disease was performed according to the RECIST criteria every 2 months until withdrawal of the study.

Left ventricular ejection fraction (LVEF) was monitored every two month using echo cardiograph, and trastuzumab treatment was suspended if LVEF decrease more than 20% comparing before treatment (even if LVEF was > 50%) or LVEF < 50%.

In a two-year period, 83 patients had been screened for HER2 status (pre-included). Fifty five of them were HER2+ (IHC or FISH).

Regarding the long term indication of trastuzumab in HER2+ MBC patients, the development of new chemotherapeutic associations with this agent and the cost of a long term targeted therapy, the HER.M.E.S group try to identify early predictors of therapeutic efficacy. H-ECD appears regarding literature to be a good candidate and the potential impact of H-ECD monitoring was prospectively included. In a two year period, 83 patients have been pre-included. Sixty five of them were HER2+ (IHC or FISH). Mean age was 53.6 years. Eighty percent of the patients received adajunt chemotherapy treatment. H-ECD level was 238 ng/mL (median) in HER2 over expressed population (n=65).

Results

Considering patients who could be pre-included in the study if the HER2 status was not known, all MBC patients didn't have tumours with HER2 over expression. Nevertheless using Wilcoxon-test there was a correlation (p=0.008) between HER2 over expressing (FISH and/or IHC) and H-ECD levels (upper limit of normal < 15 ng/mL). Looking the metastatic spread of the disease, H-ECD levels seems to be strongly correlated with the number of metastatic sites (p= 0.004, Wilcoxon-test). These results seem equal to those previously published (1,3). H-ECD could be an important parameter for early diagnosis and spread of metastatic disease in patients with HER2 over expressed tumours.

Conclusions and discussion

Trastuzumab is an essential treatment for patients with HER-2 over expressing tumours with an impact on overall survival (4). Recently it was demonstrated that early administration of trastuzumab could favourably impact overall survival of these population (5).

However preliminary results suggest efficiency of different protocols associating trastuzumab and chemotherapy. For clinicians, the usefulness of a new marker in HER2 population could be of great interest helping strategies decisions in this population of patients.

Regarding the preliminary results of HER.M.E.S trial, H-ECD level seems very interesting because of:

• High sensitivity and specificity
• Targeting for therapy
• Prognosis
• Early prediction of treatment response

Some informations are needed to specify the place of H-ECD routinely.

Does decrease of ECD predict TTP better than other parameters ?

It doesn't seem that the monitoring of follow-up and therapy effects could be definitely done just by H-ECD levels.

The economical impact of H-ECD monitoring is ongoing and final analyses will be presented when the patients follow-up will be relevant.

Bibliography