Évolution des traitements médicaux
Thérapie adjuvante anti-Her2 : nouvelles données

Adjuvant anti-HER2 therapy: new data

Mots-clés : Trastuzumab - Adjuvant - Chimiothérapie.
Keywords: Trastuzumab - Adjuvant - Chemotherapy.

E. Perez*

Récemment, les résultats impressionnants intégrant la thérapie anti-HER2 en tant que partie du traitement adjuvant pour les patients atteints de cancer du sein résecté sont basés sur une sélection optimale des patients en fonction des caractéristiques cliniques et des marqueurs de réponse du tissu. [Perez et al., 2006; Paik et al., 2005]. Le contrôle de la qualité, par immunohistochimie ou analyse génétique de HER2, est critique pour la sélection des patients.

Update of results of major adjuvant trastuzumab studies

Les essais intergroupe et NSABP B-31 en cours évaluent le rôle d’ajouter Trastuzumab (H) au régime AC-T pour les patients avec cancer du sein résecté, positif ou à haut risque de node negatif (patients n’ayant pas de ganglions.node posiitifs) avec HER2 suréproussé ou amplifié [Romond, Perez et al., NEJM 2005]. HERA (HERceptin Adjuvant) évalue l’effet adjuvant de Trastuzumab après la fin de la chimiothérapie (avec ou sans radiothérapie) [Piccart et al., 2005; Smith et al., 2006]. Le BCIRG 006 évalue l’avantage de deux regimens de Trastuzumab dans le cancer du sein amplifié par HER2 et inclut deux bras contenant de l’anthracycline [Slamon et al., 2005]. Les résultats récemment rapportés de ces essais démontrent des bénéfices impressionnants de DFS (dans tous les essais) et de survie globale (OS) (dans l’analyse jointe de N9831 et B-31) avec les traitements chimiothérapie-trastuzumab vs chimiothérapie seule.

* Mayo Clinic, Jacksonville, Floride, États-Unis.
N9831 enrolled patients into one of three arms: Arm A was doxorubicin plus cyclophosphamide (AC) followed by paclitaxel (T), Arm B was AC followed by T, followed by trastuzumab (H) (sequential treatment), and Arm C was AC followed by TH (concurrent treatment) [Perez et al., 2005]. NSABP B-31 enrolled patients into one of two arms: AC followed by T or AC followed by TH. A joint analysis of the AC followed by T vs the AC followed by TH arm at a median follow-up of 2 years is available for these 2 trials [Romond, Perez et al., NEJM 2005]. In the HERA trial, following the completion of chemotherapy, patients were randomized to H for 1 year, H for 2 years, or observation. Data are available at a median follow-up of 2 years for the HERA trial [Smith et al., 2006]. The BCIRG trial includes 2 anthracycline arms, 1 with concurrent trastuzumab and taxane, and a trastuzumab-nonanthracycline regimen. Median follow up at the time of the most recent report (December 2005) was 23 months [Slamon et al., 2005].

In the joint analysis of N9831 and NSABP B-31, DFS was 85% at 4 years for patients treated with AC followed by TH, compared with 67% in the control arm of AC followed by T (HR: 0.48, IC95: 0.39 to 0.59; p < 0.0001) [Romond, Perez et al., NEJM 2005]. Findings in the HERA trial were consistent with those of the joint analysis. HERA reported a 2-year DFS of 86% after 1 year of trastuzumab vs 77% after 1 year of observation (HR: 0.54, IC95: 0.43 to 0.67; p < 0.0001) [Piccart-Gebhart et al., 2005]. In both the joint analysis and the HERA trial, all evaluated subsets derived a strong relative benefit from trastuzumab. There was a statistically significant improvement in distant disease-free survival (DDFS) as well, with a hazard ratio (HR) for DDFS of 0.47 (IC95: 0.37 to 0.61; p < 0.0001) in the joint analysis and 0.49 (IC95: 0.38 to 0.63; p < 0.0001) for the HERA trial. The joint analysis reported a 33% decrease in mortality with trastuzumab (HR: 0.67, IC95: 0.48 to 0.98; p = 0.015). Moreover, the HERA trial has now demonstrated an OS at a median follow up of 2 years (HR: 0.76, p = 0.26) [Romond, Perez et al., NEJM 2005; Smith et al., 2006]. When the results of N9831 are looked at individually, they suggest that concurrent therapy may be superior to sequential therapy, and not associated with more cardiotoxicity [Perez et al., 2006]. Moreover, cardiac safety of concurrent radiation with trastuzumab were reported from N9831 [Halyard et al., 2006].

**Optimal duration of adjuvant trastuzumab**

The ideal duration of trastuzumab administration is under investigation, although most of the beneficial data reported so far are based on 1 year therapy. Recent provocative data in a very small number of patients suggest that even short-term trastuzumab may be effective in preventing recurrence.

The results of the recently reported FinHER adjuvant therapy trial [Joensuu et al., 2006] demonstrate that trastuzumab plus a taxane or vinorelbine for 9 weeks followed by three 3-weekly cycles of FEC is well tolerated and effective in preventing recurrence of ErbB2 amplified breast cancer. However, the IC95 for the hazard ratio for recurrence-free survival is quite wide (0.21-0.83), and based on only 27 events in the two non-
trastuzumab arms and 12 events in the two trastuzumab arms. The question of shorter
duration of trastuzumab of less than one year is now being addressed by the French
Breast Group, in a trial initiated in 2006. These investigators plan to enroll 8000 women
to receive either 6 months or 12 months of trastuzumab after completing chemotherapy
and radiation as indicated.

**Additional anti-HER2 strategies beyond trastuzumab**

Despite the impressive results of the recently released trastuzumab adjuvant therapy
trials, 15% of patients with HER2 overexpressing or amplified breast cancer developed
tumor relapse at 3 years, and there is some concern related to site-specific metasta-
ses—including brain.

Several pan-HER or dual HER inhibitors are at different stages of development, but
lapatinib is the most advanced. Lapatinib is a reversible tyrosine kinase inhibitor (TKI)
that potently inhibits both ErbB1 and ErbB2 tyrosine kinase activity. In breast cancer
cell lines (with 100-fold selectively for cancer cells vs a normal human cell line) treated
with lapatinib, growth arrest and cell death were observed. Lapatinib also selectively
inhibits tumor xenograft growth in a dose-dependent manner [Rusnak et al., 2001]. In a
pilot study conducted in patients with metastatic tumors overexpressing ErbB2 and/or
expressing ErbB1, biopsy specimens from responders treated with lapatinib exhibit
increased apoptosis, while specimens obtained from non responders did not [Spector,
Xia et al., 2005].

This agent has undergone preclinical, phase I, pharmacokinetic, as well as phase II
and III evaluation in the setting of HER2 positive metastatic breast cancer, with impres-
sive data. Pharmacokinetics data show incomplete and highly variable oral absorption
that increases with food, metabolism primarily by CYP 3A4/5, and a half-life of approxi-
mately 24 hours.

The single agent activity of lapatinib has been demonstrated in phase II studies of
patients previously treated with trastuzumab, but also in patients who had not received
trastuzumab.

Although both trastuzumab and lapatinib inhibit the same receptor, ErbB2, the
combination is potentially attractive because each agent targets a different part of the
receptor, with trastuzumab targeting the extracellular domain and lapatinib the intra-
cellular domain. In addition, they appear to have different mechanisms of action, with
trastuzumab activity at least in part due to increased internalization and degradation
of ErbB2 and lapatinib inhibiting the ErbB2 tyrosine kinase. This differentiation may
lead to sustained inhibition of activation of the receptors, and possibly to enhanced
inhibitory signals.

Currently, there are several phase III studies ongoing to evaluate lapatinib in patients
with metastatic breast cancer. The EGF100151 randomized, open-label trial is com-
paring capecitabine with and without lapatinib in patients with HER2 overexpressing
disease who have been previously exposed to anthracycline, taxane, and trastuzumab. The study yielded a highly statistically significant improvement in time to progression for the patients assigned to capecitabine plus lapatinib compared to those who received capecitabine alone, in the range of 5 months [Geyer et al., ASCO 2006].

An analysis of cardiac safety of lapatinib was also presented at ASCO 2006 [Perez et al., 2006]. The data were based on more than 3000 patients enrolled to lapatinib trials, approximately half of them with breast cancer, who had received anthracyclines and/or trastuzumab. The other half of the patients had tumor types different than breast and had not received trastuzumab. Evaluation of cardiac ejection fraction was made every 2 months, added to clinical follow up. The results demonstrate only a 1.3% of decreases of LVEF and a rate of symptomatic cardiac events of only 0.1%. These data demonstrate that this agent appears to be quite safe from the cardiac standpoint, although additional follow up is ongoing.

Data from ongoing trials, added to our improved understanding of targeted therapies allows us an opportunity to develop new translational trials to improve outcomes in patients with resected HER2+ breast cancer. Patient follow up from all of the reported trastuzumab adjuvant trials will continue, concentrating on long term efficacy, safety especially cardiac), correlative studies of clinical characteristics with outcome, as well as translational studies of molecular tumor markers with response. Some of these markers include c-myc, PTEN, topoisomerase II alpha, cyclin D1, IGFR-1, amongst others.

Trials are being developed on a worldwide basis, incorporating adjuvant lapatinib. Some of the issues to be explored in these studies include: Efficacy of lapatinib alone, lapatinib in combination with trastuzumab, or sequential use of lapatinib followed by trastuzumab (in the setting of appropriate chemotherapy – with the patients starting trastuzumab preferably concurrent with taxane in view of preclinical data, results in the metastatic setting, as well as data from Perez et al as part of N9831. In addition, “recurrence samples” will be collected, when available, in order to better understand the biology of disease that recurs during or soon after HER2-directed therapy. This collection will also give us insight as to differences between resistance to trastuzumab, lapatinib, the combination of trastuzumab and lapatinib and may suggest novel therapeutic strategies. Safety and quality of life issues will also be important part of new studies.

Références bibliographiques


• Jones SF, Burris HA, Yardley DA et al. Lapatinib (an oral dual kinase inhibitor) plus weekly or every 3 week paclitaxel. Breast Cancer Res Treat 2004;88(Suppl. 1):S64.


• Rusnak DW, Lackey K, Affleck K et al. The effects of the novel, reversible epidermal growth factor receptor/ERbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human normal and tumorderived cell lines in vitro and in vivo. Molec Cancer Therap 2001;1:85-94.


• Smith I. Trastuzumab following adjuvant chemotherapy in HER2-positive early breast cancer (HERA Trial): Disease-free and overall survival after 2 year median follow-up. Presented at: American Society of Clinical Oncology Annual Meeting Scientific Special Session; June 3, 2006; Atlanta, Georgia.
Thérapiadjuvante anti-HER2 : nouvelles données