ADYUDANCIA CON TRASTUZUMAB (HERCEPTÍN^{R}) EN CA. MAMA. REVISIÓN REDUCIDA.

De Felipe O, Ojeda F*
Servicio de Ginecología y Obstetricia. Fundación Hospital de Alcorcón.
*Servei de Ginecologia i Obstetrícia. Fundació Hospital Asil de Granollers

El trastuzumab es un anticuerpo monoclonal murino humanizado anti-HER2 que presenta una alta afinidad y especificidad inhibiendo la señal de traducción de la proteina HER2, en la página: http://www.her2.roche.es/ pueden encontrar toda la información complementaria respecto a HER-2 y como determinar el *status* de la paciente respecto a este marcador.

Es necesario explicitar la positividad el HER2 en el cáncer de mama ya que su positividad determina una mayor agresividad del tumor.

Las pacientes HER2 positivas se consideran de alto riesgo y mal pronóstico, así mismo, se ha determinado su valor predictivo: las pacientes HER2 positivas presentan una mejor respuesta con Inhibidores de la aromatasa que con tamoxifeno.

Los ensayos más conocidos son:

HERA	BCIRG 006
NSABP-B31	NCCTG Nº 9831

Los resultados globales se resumen a continuación:

-El herceptín mejora la curva de Supervivencia libre de enfermedad (SLE) con disminución significativa del riesgo de recidiva tras el empleo de la quimioterpia (QT) pero no mejora de forma significativa la Supervivencia global (SG) aunque existe una tendencia a mejorarla (expectativa futura).

-El riego de recidiva disminuye en el tiempo al asociar herceptín y la QT.

-El tratamiento concurrente del trastuzumab con la QT podría ser mejor que la secuencial ya que estimula el efecto apoptótico de la QT (acción sinérgica observada en estudios de experimentación animal).

-Se desconoce la duración óptima del tratamiento: recomiendan un año o hasta 6 meses posterior a la finalización de los tratamientos convencionales.

Respecto a los efectos secundarios de la terapia:
Cardiotoxicidad (insuficiencia cardiaca congestiva) con tratamiento concurrente o posterior al empleo de antraciclinas (estudio N9831: aumenta de forma significativa el número de eventos cardiacos al tratamiento concomitante desde los 6 meses de inclusión).
La radioterpia asociada de forma secuencial o concomitante al tratuzumab no aumenta el riesgo de eventos vasculares.
El grado de reversibilidad de la cardiotoxicidad es incierto. Se desconocen los efectos a largo plazo.

-Perspectivas de Futuro:
Se esta estudiando la asociación de tratuzumab® con anti-VEGF , anti- factor de crecimiento endotelial (estudio E2100), para mejorar los resultados.

Referencias de interés:

http://www.heratrial.com/index.htm **HER**ceptin® **A**djuvant Trial

http://www.bcirg.org/Internet/Studies/BCIRG+006.htm BCIRG 006 (GMA TAX302)

http://www.breastcancer.org.uk/bulletins/e-bulletin3.pdf NSABP-B31

Romond EH, Perez EA, Bryant J, et al. Advances in monoclonal antibody therapy for breast cancer: Combines analysis of NSABP-B31/NCCTG-N9831. American Society of Clinical Oncology Annual Meeting. Orlando, FL, 2005. http://www.asco.org

Real-World Performance of HER2 Testing - National Surgical Adjuvant Breast and Bowel Project Experience
Paik S, Bryant J, Tan-Chiu E, Romond E, Hiller W, Park K, Brown A, Yothers G, Anderson S, Smith R, Wickerham DL, Wolmark N
Journal of the National Cancer Institute 94(11):852-854, June 5, 2002
Abstract
Trastuzumab (Herceptin) provides clinical benefits for patients diagnosed with advanced breast cancers that have overexpressed the HER2 protein or have amplified the HER2 gene. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-31 is designed to test the advantage of adding Herceptin to the adjuvant chemotherapeutic regimen of doxorubicin and cyclophosphamide followed by paclitaxel (Taxol) in the treatment of stage II breast cancer with HER2 overexpression or gene amplification. Eligibility is based on HER2 assay results submitted by the accruing institutions. We conducted a central review of the first 104 cases entered in this trial on the basis of immunohistochemistry (IHC) results. We found that 18% of the community-based assays, which were used to establish the eligibility of patients to participate in the B-31 study, could not be confirmed by HercepTest IHC or fluorescence in situ hybridization (FISH) by a central testing facility. This report provides a snapshot of the quality of HER2 assays performed in laboratories nationwide.
National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA, USA.
Moving Forward: Herceptin in the Adjuvant Setting

Tan-Chiu E, Piccart M. Oncology 63 Suppl 1:57-63, 2002
Abstract
HER2 overexpression/amplification, which is an early event in breast cancer development, is associated with a poor prognosis and may predict response to therapy. Herceptin, an anti-HER2 monoclonal antibody, has shown significant efficacy in the treatment of HER2-positive metastatic breast cancer and appears to provide greater benefit the earlier the drug is given. Moreover, Herceptin also demonstrates a favorable safety profile and is associated with quality-of-life benefits. Taken together, these factors provide the rationale for moving this

drug into the adjuvant setting, and four large-scale trials that will involve a total of more than 12,000 women with HER2-positive primary breast cancer have been undertaken to address this issue. In the United States, NSABP trial B31 and the Intergroup N9831 trial will investigate Herceptin in combination with the standard US regimen of anthracycline/cyclophosphamide followed by paclitaxel. Trial BCIRG 006, which is being conducted globally, will examine Herceptin in combination with platinum salts/docetaxel. The HERA Trial, involving countries outside the US, will examine q3-weekly Herceptin monotherapy given for 1 and 2 years after the completion of adjuvant chemo-/radiation therapy. The breadth of the ongoing Herceptin adjuvant trials will potentially allow the optimal treatment approach to be identified.
Cancer Research Network Inc., 350 NW 84th Avenue, Suite 305, Plantation, FL, USA.

The NCCTG 9831 Trial
Similar to the NSABP B-31 trial, the North Central Cancer Treatment Group (NCCTG) 9831 intergroup randomized trial is evaluating whether the addition of trastuzumab to chemotherapy adds benefit to patients with node-positive disease in the adjuvant setting. In the trial protocol, trastuzumab therapy begins immediately following (with weekly paclitaxel) or 3 months after (following 12 weekly doses of paclitaxel) the completion of four cycles of conventional doxorubicin and cyclophosphamide (AC) and these are compared with a control arm without trastuzumab. The projected accrual to these three arms is 3,000 patients with node-positive disease. In January 2002, patient enrollment to the arm combining paclitaxel with trastuzumab immediately after AC was temporarily suspended following an interim safety analysis due to concerns of an apparently greater risk of congestive heart failure. This was not subsequently confirmed, and that study arm has since been reopened to patient enrollment.
http://www.natlbcc.org/bin/index.asp?strid=780&depid=9 Analisis de ambos NSABP B31 y NCCTG

Table 1: Trastuzumab Adjuvant Trial Designs

NSABP B31	AC x 4	Paclitaxel q3w x 4	
	AC x 4	Paclitaxel q3w x 4 + T qw for 52 weeks	
NCCTG	AC x 4	Paclitaxel qw x 12	
N9831	AC x 4	Paclitaxel qw x 12T qw for 52 weeks	
	AC x 4	Paclitaxel qw x 12 + T qw for 52 weeks	
BCIRG 006	AC x 4	Docetaxel q3w x 4	
	AC x 4	Docetaxel q3w x 4 +	TqwTq3w
	carboplatin + docetaxel q3w x 6 + Tqw		Tq3w1 year
HERA TrialAny	CT ± RT	T q3w x 1 year	
		T q3w x 2 years	
		Observation	
FinHer trial	Vinorelbine x 4	± T x	FEC x 3
	Docetaxel x 4	9 wks	

Abbreviations: NSABP =National Surgical Adjuvant Breast and Bowel Project; NCCTG= North Central Cancer treatment Group; BCIRG Breast Cancer International research Group; HERA=Herceptin adjuvant; Fin Her= Finnish trial; AC=doxorubicin and cyclophosphamide; T=trastuzumab; q3w=every 3 weeks; qw=weekly; CT=chemotherapy, RT=radiotherapy; FEC=5-fluorouracil,epirubicin, cyclophosphamide

http://www.asco.org/portal/site/ASCO/menuitem.64cfbd0f85cb37b2eda2be0aee37a01d/?vgnextoid=09f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=vm_session_presentations_view&confID=34&presentationID=5816
Advances in Monoclonal Antibody Therapy for Breast Cancer. Simposium ASCO 2005.