

## TRASTUZUMAB IN THE TREATMENT OF ADVANCED BREAST CANCER.

OUR SINGLE-CENTER EXPERIENCE AND SPOTLIGHTS OF THE  
LATEST NATIONAL CONSENSUS MEETINGADRIANA TOMADONI<sup>1</sup>, DIANA LOMBARDO<sup>2</sup>, RAUL WAINSTEIN<sup>1</sup><sup>1</sup>Servicio de Oncología, <sup>2</sup>Servicio de Anatomía Patológica, Hospital Nacional Profesor Alejandro Posadas, El Palomar, Provincia de Buenos Aires.

**Abstract:** Human epidermal growth factor receptor (HER 2) is amplified in 25 to 30% of breast cancer patients and those whose tumors demonstrate HER 2 gene amplification and protein overexpression have an inferior prognosis manifested by shorter disease-free and overall survival. Trastuzumab, the humanized murine anti-HER 2 monoclonal antibody, inhibits tumor growth when used alone and has synergistic and additive effects when used with chemotherapeutic agents (paclitaxel-doxorubicine). At the present time, the accurate diagnostic assessment of HER 2 is essential for appropriate application of the humanized anti HER 2 monoclonal antibody, trastuzumab, for the treatment of patients with metastatic breast cancer. FDA has approved its use for patients with metastatic breast cancer with HER 2 over-expression since 1998, as a first line treatment in association with paclitaxel or as a second or third line monotherapy. In Argentina, two Consensus Meetings of HER 2 Diagnosis have taken place: the first one on May 15th, 2002 and the second on April 11th, 2003, supported by Roche Laboratories (Herceptin®). In this paper, some topics of these meetings are reviewed. Our single-public center experience is discussed.

**Key-words:** trastuzumab, breast cancer, Her 2, diagnosis

**Resumen:** *Trastuzumab en el tratamiento del cáncer de mama avanzado. Nuestra experiencia y aspectos de la última Reunión Nacional de Consenso.* El receptor para el factor humano de crecimiento epidérmico (HER 2) se encuentra amplificado en el 25 a 30% de los cánceres de mama y aquellas pacientes con tumores que amplifiquen el gen HER 2 y sobreexpresen su proteína tienen un peor pronóstico que se traduce en menor supervivencia global y tiempo libre de enfermedad. Usado como monodroga, Trastuzumab, el anticuerpo monoclonal murino humanizado anti-HER 2, inhibe el crecimiento tumoral y posee efectos sinérgicos y aditivos cuando se agrega a otros agentes quimioterápicos (paclitaxel-doxorubicina). La determinación diagnóstica precisa del HER 2 es esencial para establecer el uso racional de trastuzumab en el tratamiento de pacientes con cáncer de mama metastático. La FDA aprobó su uso para pacientes con cáncer de mama metastático que sobreexpresen el HER 2 desde 1998, como primera línea terapéutica asociado a paclitaxel o como monodroga en segunda o tercera líneas. En Argentina, se realizaron dos Reuniones de Consenso para Diagnóstico de HER 2: la primera el 15 de mayo de 2002 y la segunda el 11 de abril de 2003, auspiciadas por Laboratorios Roche (Herceptin®). En esta publicación, exponemos los temas destacados de ambos encuentros. Discutimos también nuestra experiencia en la determinación de HER 2 y tratamiento con trastuzumab.

**Palabras clave:** trastuzumab, cáncer de mama, Her 2, diagnóstico

A growth factor receptor gene, human epidermal growth factor receptor (HER 2), is amplified in 25 to 30 percent of breast cancers and in these cases the encoded protein is present in abnormally high levels in the malignant cells<sup>1</sup>. Patients whose tumors demonstrate HER

2 gene amplification and protein overexpression have an inferior prognosis manifested by shorter disease-free and overall survival<sup>2</sup>. The American Society of Clinical Oncology has emphasized the importance of the determination of HER 2 overexpression in every patient with breast cancer at the moment of the initial diagnosis or upon its recurrence<sup>3</sup>. Trastuzumab is a biological anticancer agent. This humanized murine anti-HER 2 monoclonal antibody inhibits tumor growth when used alone and has synergistic and additive effects when used with chemotherapeutic agents (paclitaxel-doxorubicine). Recent clinical trials implicating HER 2 in modified

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**Dirección postal:** Dra. Adriana Tomadoni, Lafuente 723, 1406 Buenos Aires, Argentina.

Fax: (54-11) 4469-9200

e-mail: gbernal@intramed.net.ar

responses to anti-estrogens and anthracyclins<sup>4, 5</sup> have stimulated interest in accurate and reliable identification of patients with carcinomas driven by HER 2 amplification and overexpression<sup>6</sup>, although these findings remain unconfirmed at present by prospective clinical trials<sup>7</sup>. However, the accurate diagnostic assessment of HER 2 is essential for appropriate application of the humanized anti HER 2 monoclonal antibody trastuzumab to the treatment of patients with metastatic breast cancer. In fact, FDA approved its use for patients with metastatic breast cancer with HER 2 overexpression since 1998 as a first line treatment in association with paclitaxel or as a second or third line monotherapy<sup>8</sup>.

Vogel et al.<sup>9</sup> conducted a randomized clinical trial to evaluate the efficacy and safety of first line, single-agent Trastuzumab in women with HER 2-overexpressing metastatic breast cancer. The results showed an objective response rate of 26%, and no benefits for those women with 2+HER 2 overexpression.

Slamon et al.<sup>10</sup> in his randomized clinical trial, used Trastuzumab in combination with paclitaxel. The trial showed that trastuzumab increases the clinical benefit of first-line chemotherapy in metastatic breast cancer that overexpresses HER 2. The addition of trastuzumab to chemotherapy was associated with longer time to disease progression (median, 7.4 vs. 4.6 months), a higher rate of objective response (50% vs. 32%), a longer duration of response (median, 9.1 vs. 6.1 months) and a low rate of death at one year (22% vs. 33%).

The recommended dose of trastuzumab as single or combined agent is a standard loading dose of 4mg/kg followed by 2mg/kg weekly<sup>11</sup>. If objective response is achieved, the agent must be followed until toxicity, progression or death. The most important reported adverse event is cardiac dysfunction. It is dose independent and mostly reversible after drug discontinuation<sup>12</sup>. In fact, trastuzumab should be discontinued if significant heart failure develops. The incidence is greatest in patients receiving concomitant trastuzumab with

anthracycline plus cyclophosphamide (27%). It is substantially lower in those receiving paclitaxel and trastuzumab (13%) or trastuzumab alone (3 to 7%). Most trastuzumab-treated patients developing cardiac failure are symptomatic (75%). The most common treatment-related adverse events are chills, asthenia, fever, pain and nausea<sup>13</sup>. Trastuzumab is available in vials of 440mg which cost \$ 4,700.

The debate about which diagnostic system is the most accurate for the determination of the HER 2 status of a patient's tumor is a frequent topic of discussion among pathologists<sup>7, 14, 15</sup>. Briefly: the methods available for determination of HER 2 over-expression are: Immunohistochemical studies (IHC): Herceptest (*Dako, Inc.*), Pathway (*Ventana, Inc.*).

Fluorescence in situ hybridization (FISH): PathVysion (*Vysis, Inc.*). Although, based on current literature, FISH detection of HER 2 gen amplification may provide more accurate information in the selection of patients for treatment with targeted therapies such as Trastuzumab but this method is not yet widely available. The cost of each determination for a private patient is around \$550. Therefore, screening by IHC for HER 2 protein, backed by rigorous quality controls and FISH testing of equivocal cases with intermediate staining intensity, remains the current practice. The different test kits for HER 2 protein determination (each targeting different epitopes on the HER 2 receptor) cost from \$4,980 to \$995. Each kit is used for 30 or 35 determinations. The cost of each determination goes from \$175 to \$ 50. An important factor in correlation between Herceptest<sup>®</sup> and FISH results is the experience of the pathologic centre. Discrepancies are greatest for small local laboratories.

To achieve acceptable levels of performance it will be important for laboratories initiating their own analyses to gather experience of testing and scoring of tumors on training sets and to participate regularly in a quality assurance scheme<sup>16, 17</sup>. In our country two Consensus Meetings of HER 2 Diagnosis took place: the first one on

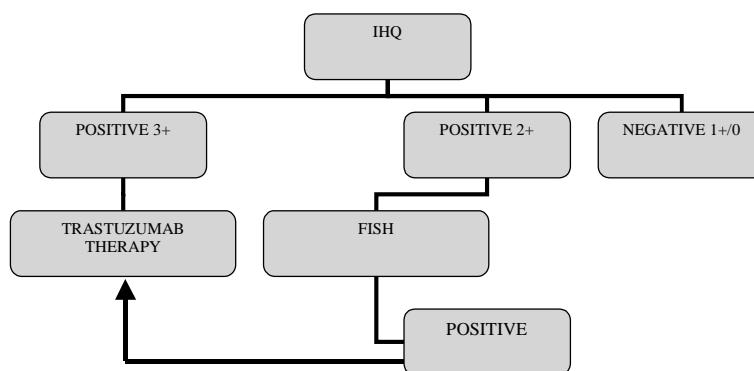


Fig. 1.– Algorithm for Trastuzumab use. Consensus Meeting HER2, March 15<sup>th</sup>, 2002

May 15th, 2002 and the second on April 11<sup>th</sup>, 2003, supported by Roche Laboratories (Herceptin®)<sup>18</sup>. In both two, the Consensus determined:

- When and who assess HER 2 status?: When trastuzumab could be a treatment choice or when testing for HER 2 status could be particularly relevant if a new chemotherapy line should be considered (anthracycline-based therapy).

- Recommended methods: IHC or FISH. There were also suggestions regarding antibodies/probe; sample preparation; what to report; score IHC; IHC interpretation; FISH methodology. Finally an algorithm for Trastuzumab use was suggested (Fig. 1).

one patient had her HER2 test carried out by FISH method in an external laboratory (Fig. 2).

**Methods**

We observed strict adherence to the manufacturers instructions. The guidelines for scoring were those recommended in the first National Consensus Meeting<sup>18</sup>:

- 0/1+ Negative
- 0: no staining or less than 10% of tumoral cells staining.
- 1+: weak staining, less intense staining in more than 10% of tumoral cells. Cells with parcial membrane staining.
- 2+/3+ Positive
- 2+: weak to moderate complete membrane staining in more than 10% of the malignant cells.
- 3+: strong and complete membrane staining in more than 10% of the malignant cells.

**Our experience**

The National Hospital Profesor Alejandro Posadas is a policlinic center of 550 beds in the western outskirts of Buenos Aires city. The Oncology Department receives 12.000 consultations per year and 4000 chemotherapeutic treatments are carried out in its Daily Hospital.

**Materials and Methods**

*Materials*

During 2001, we used a Herceptest kit (IHC- Dako, Inc.) to determine HER2-overexpression in premenopausal women with metastatic breast cancer with a negative estrogenic receptor status. Positive HER2 status rendered them eligible for second or third line treatment with tratuzumab alone or with paclitaxel. Thirty determinations were done using recent samples or archival histopathological blocks. In the meantime,

**Results**

From these 31 patients, 23 (74.19%) were negative: 17=0 (73.9%); 6=1+ (26%). Eight (25.8%) proved to be positive: 6=3+ (75%); 2=2+ (25%, one of them by FISH). We decided that the six patients with HER2 +++ and the one with ++ by FISH were to receive trastuzumab as monotherapy (n=3) or in combination with paclitaxel (n=3). The patient with ++ by IHC was to confirm the result with a FISH test (Table 1). From the seven patients to whom we prescribed Trastuzumab, six got the drug: 4 through their medical insurance, one through the Public Health Ministry and the last through the Ministry the first time and by her medical insurance afterwards. One patient never got the drug.

From these six patients: 3 (50%) received trastuzumab during eight months or more, since their complete response last from 8 to 24 months and the drug was administered once weekly all over this period of no

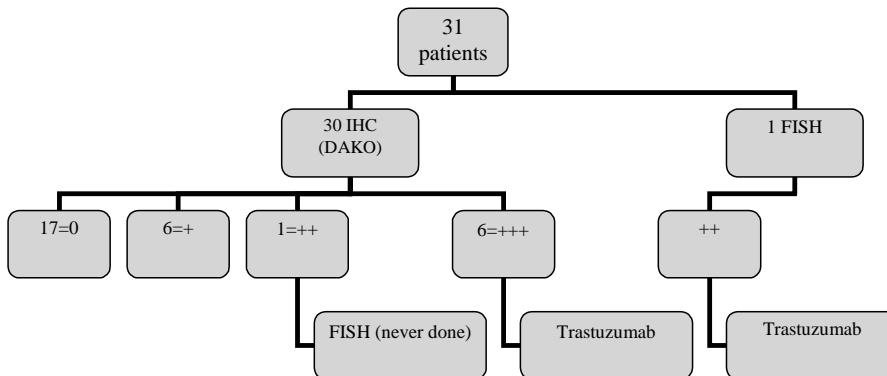


Fig. 2.- Diagnostic algorithm.

TABLE 1.– Patients receiving Trastuzumab

Patient	Age	Metastatic site	Time with Trastuzumab (months)	Response	Adverse effects	Drug discontinuation due to
1	29	lungs, skin, contralateral axillary nodes	24	complete	no	progression
2	42	skin, contralateral axillary nodes	18	complete	flushes, ↑ HT* ↓ LVE**	↓ LVE**
3	39	bone	8	complete		progression
4	45	lung	7	complete		progression
5	47	bone, lung	7	complete		progression
6	37	bone, lung	2	progression		progression

\*hepatic transaminases elevation. \*\*decline in the left ventricular ejection fraction

evidence of disease. The other three had partial response of short duration (n=2) or no benefit at all (n=1).

In one patient we observed: hot flushes in the cheeks during the loading dose, transient hepatic transaminases elevation that did not require additional intervention or discontinuation of the treatment and a decline in the left ventricular ejection fraction measured in the regular monitoring without clinical expression. In this case trastuzumab was discontinued. No treatment-related adverse events were registered in the other patients.

## Discussion

According to the published data and our preliminary experience, trastuzumab therapy showed promising results in a percentage of women with metastatic breast cancer over-expressing HER 2, that is: approximately 25% of all patients with metastatic breast cancer. It proved to be a safe, active and well-tolerated biological treatment. The main difficulties registered in a public general hospital were:

1) To obtain the experience and training of the involved personnel depended on having the diagnostic test kits available to do a reasonable number of assays a year to ensure the quality of the results. The economic factor was one but not the only limitation point. In part, this could be solved by sending the samples to another referential center which kindly do the tests.

2) To use the FISH method to retest the ambiguous cases (HER 2=2+) since it is not yet widely available.

3) Trastuzumab was difficult to obtain from certain medical insurances and from public sources.

4) Handling the anxiety and frustration of patients and relatives who did not get the drug in the proper way and time was not a minor problem in our daily clinical practice.

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*Along the way, I learned how important it can be to have great personal resolve, to cultivate colleagues, to ignore convention, and to look for new vistas. The last of these –the search for new vistas– should hold a special place in the lives of young scientists. I was privileged to participate in the birth and maturation of two research fields, and in both, the great exaltations came mainly in the beginning. It is the pioneers in science who have most fun (albeit not always the most fame).*

En el camino, aprendí lo importante que es tener poder de decisión, cultivar colegas, ignorar convenciones, y buscar nuevos horizontes. Esto último –la búsqueda de nuevos horizontes– tendría que ocupar una parte especial de la vida de los jóvenes investigadores. Tuve el privilegio de participar en el nacimiento y desarrollo de dos campos de investigación, y en ambos, los grandes júbilos surgieron sobre todo al principio. Son los pioneros en ciencia los que más se divierten (y no siempre los que adquieren más fama)

J. Michael Bishop

*How to Win the Nobel Prize: An unexpected Life in Science.*  
Cambridge MA: Harvard University Press, 2003, p 58