Trastuzumab as an Adjuvant Therapy for HER-2-Positive Breast Cancer

a report by
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Trastuzumab (Herceptin®) is a humanized monoclonal antibody that binds to the extracellular domain of human epidermal growth factor receptor (EGFR) 2 (HER-2), which is overexpressed and/or amplified in 20–30% of breast cancers. These tumors, without systemic treatment, show a more aggressive behaviour. In the metastatic breast cancer setting, in the subgroup of patients with tumors that overexpress HER-2, trastuzumab has proven to be an active drug both as a single agent and in combination with chemotherapy, modifying the natural history of these tumors even if approximately one out of two patients obtains a clinical response. Based on these results trastuzumab has been utilized in adjuvant trials. Recently, the results of five adjuvant trials have been reported, showing a 50% reduction of the relative risk of recurrence. The design of these trials is shown in *Table 1*.

Two of these trials have been carried out in the USA and are the North American Surgical Adjuvant Breast and Bowel Project (NSABP) B31 and the North Central Cancer Treatment Group (NCCTG) N9831 trials. The first one is a two-arm trial comparing four courses of doxorubicin and cyclophosphamide (AC) followed by four courses of three weekly paclitaxel with or without trastuzumab. The second is a three-arm trial exploring two different modalities of trastuzumab administration with weekly paclitaxel (concurrent versus sequential at the end of chemotherapy) after four courses of AC. The National Cancer Institute (NCI) and the US Food and Drug Administration (FDA) approved a joint analysis of the two similar arms in the two studies whose results have been reported. Two other large trials have enrolled patients from different countries and are the Herceptin Adjuvant (HERA) trial, where trastuzumab was administered for 0, one or two years every three weeks at the end of chemotherapy (any) and radiotherapy if required and the Breast Cancer International Research Group (BCIRG) 006 trial, which is a three-arm trial evaluating 4 courses of AC followed by four courses of docetaxel with or without trastuzumab and a regimen not containing anthracyclines with carboplatin and docetaxel for six courses given concurrently with trastuzumab.

The fifth trial is a small Finnish trial (FinHer), where trastuzumab is randomly administered concurrently with docetaxel or vinorelbine for only nine weeks and before three courses of fluorouracil, epirubicin, and cyclophosphamide (FEC). A total of 13,352 patients have been enrolled; however, about 3,000 patients (those enrolled in the two-year arm of trastuzumab in the HERA trial and those in the sequential arm in the NCCTG N9831 trial) have not been included in this analysis. There are several differences among the five trials: the definition of high-risk node-negative patients that were eligible in all trials except in the NSABP B31; the definition of HER-2 status; the modalities of administering chemotherapy and trastuzumab (concurrent or sequential) and radiation therapy and trastuzumab (concurrent or at the end); the type of chemotherapy (i.e. only 26% of patients in the HERA trial received taxane-based regimens); the duration (from nine weeks to two years) and the schedule (weekly or three-weekly) of trastuzumab administration. In all trials half of the enrolled patients were younger than 50 years and had hormonal receptor-positive tumors. The proportion of node-negative patients was low in the NCCTG N9831 trial (5.7%) and in the FinHer trial (16%), while it represented about a third of patients in the HERA and BCIRG 006 trials.

The median follow-up ranged from 23 months in the BCIRG 006 trial to 36 months in the FinHer trial. For the HERA trial the results refer to the comparison between observation and trastuzumab for one year. Despite these differences, a highly statistically significant reduction in the rates of recurrences (from 39% to 58%) was observed in all trials and of distant recurrences. A statistically significant overall survival benefit has currently been reported in the joint analysis of the two American trials and in the HERA trial at a median follow-up of two years as shown in *Table 2*. These benefits were seen in all subgroups of patients.

Trastuzumab as a single agent is well tolerated and associated with a low incidence of side effects. Hypersensitivity reactions are seen occasionally and mainly with the first infusion, while severe and sometimes fatal pulmonary events are rare.

Cardiotoxicity has been the most important and

worrisome side effect associated with the use of trastuzumab. The incidence of cardiac dysfunction, specifically congestive heart failure (CHF), and the decrease of the left ventricular ejection fraction (LVEF), has been reported in 1–7% of patients treated with trastuzumab as a single agent with a higher incidence in older patients and in those pretreated with anthracycline. These cardiac dysfunctions are more common in patients treated concurrently with paclitaxel (13%) or with anthracyclines (27%). Some authors have proposed to classify this trastuzumab related cardiotoxicity as type II to differentiate it from that caused by anthracyclines since it is not dose-related, does not appear in all patients, is expressed in a broad range of severity, and is not associated with identifiable ultra structural abnormalities and seems reversible. Due to the cardiotoxicity of trastuzumab the eligibility criteria of all adjuvant trials were quite restrictive excluding women with cardiac risk factors and cardiac dysfunctions measured by echocardiography or multiple gated acquisition scanning. The time at which a normal cardiac function was required varied among the trials as well as the cardiac function assessment times during and after the trastuzumab treatment and the definition of cardiac events.

The incidence of class III–IV of the New York Heart Association CHF was very low (0.6%) in the HERA trial where trastuzumab was given at the end of chemotherapy and radiotherapy when required and in the TCH arm of the BCIRG 006 trial (0.4%). The concomitant administration of trastuzumab and a taxane after 4 courses of doxorubicin and cyclophosphamide was associated with a higher incidence of class III–IV of the New York Heart Association CHF that was 1.6% in the BCIRG 006 trial (arm ACTH) and 3.5% and 4.1% in the NCCTG N9831 and NSABP B31 trials respectively. When trastuzumab was given after the four courses of paclitaxel as in the sequential arm of NCCTG N9831 trial the incidence was 2.5%. The absence of cardiotoxicity in the FinHer trial could be due to the small number of patients enrolled in the trial or to the reverse sequence of trastuzumab administered before the anthracyclines. The cardiotoxicity seems reversible even if in the BCIRG 006 trial the drop of the LVEF observed in the arm ACTH recovers but does not seem to return to the basal value although it is above 60%. A longer follow-up of these trials and a close monitoring of the cardiac function will help to clarify the long term effect of trastuzumab.

Although the results obtained with trastuzumab in the adjuvant setting are impressive, they are still preliminary and need to be confirmed at a longer follow-up. Furthermore, there are several unanswered questions. We do not know if there are subgroups of node-negative patients for whom trastuzumab could be omitted or administered in combination with only hormonotherapy or other with small aggressive tumors for whom it should be used even if they do not fulfill the eligibility criteria of the above trials.

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

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The optimal timing for initiating trastuzumab, as well as the optimal modality of trastuzumab administration with chemotherapy (combination versus sequence) and the best schedule (weekly or every three weeks), is unknown.

It could be interesting to select patients who do not need an anthracycline-based regimen to reduce the risk of cardiotoxicity. The investigators of the BCIRG 006 trial have analyzed in a subgroup of patients (2,120 of 3,222) the co-amplification of the topoisomerase (topo) II-α gene that is located close to the HER-2 gene on chromosome 17q12-q21. Since topo II-α is inhibited by anthracyclines and is the molecular target of these drugs, its gene amplification may render the cells more sensitive to topo II-α inhibitors. The topo II-α gene was co-amplified in 35% of patients and these patients had a benefit only from anthracycline-based regimen with trastuzumab and not from the TCH arm while the benefit for patients without co-amplification of topo II-α was the same with the two regimens with trastuzumab. At the moment there is no broadly available topo II-α test but if this retrospective data was independently and prospectively confirmed it could have important clinical implications with the possibility of utilizing less cardiotoxic regimens for patients without topo II-α amplification.

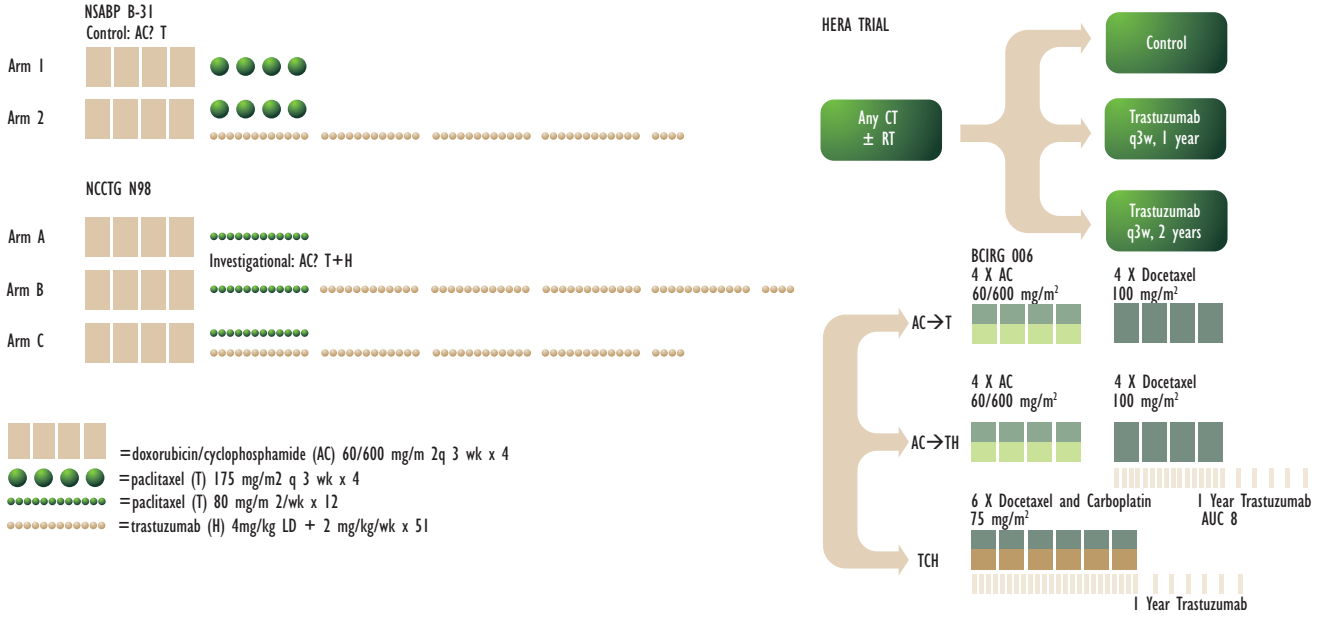
In another retrospective translational research, the co-amplification of cMyc and HER2 was observed in 25%

Table 2. Adjuvant Trials Results

	NSABP B31/N9831	BCIRG 006		HERA	FINHER
Regimen	Concurrent	Concurrent		Sequential	Concurrent
		AC(DH	DCarboH		
Follow-up, years	2	2		2	3
Evaluable patients	3351	3222		3387	232a
HR DFS	0.48*	(0.49*	0.61*	0.64*	0.42*
(95% CI)	0.39-0.59)	(0.37-0.65)	(0.37-0.65)	(0.54-0.76)	0.21-0.83
HR DDFS	0.47*	NR		0.60*	0.29*
(95% CI)	(0.37-0.61)			(0.49-0.73)	(0.13-0.64)
HR OS	0.67*	NR		0.66*	0.41
(95% CI)	(0.48-0.93)			(0.47-0.91)	(0.16-1.08)

*A HER-2 positive subgroup; *p<0.005 For the HERA trial ITT analysis since 861 out of 1,698 observation patients have chosen to switch to trastuzumab after the presentation of the outcome results in 2005.*

Figure 1: Trastuzumab: Adjuvant Trials



of patients enrolled in the NSABP-B31 trial and these patients obtained the greatest benefit from trastuzumab that seems to turn on the pro-apoptotic function of deregulated cMyc contrary to a priori hypothesis[16].

The hope is the possibility to identify molecular signatures of sensitivity or resistance to trastuzumab since adjuvant trastuzumab reduces annual hazard ratio by one-half and about half of patients with metastatic breast cancer progress despite trastuzumab treatment and the majority who achieve an initial response to trastuzumab-based regimens develop resistance within one year. There are several potential molecular mechanisms of both de novo and acquired resistance to trastuzumab, including: (1) sub-optimal drug delivery; (2) altered target expression but current preclinical data suggest continued overexpression of unaltered HER-2 protein and mRNA and clinical data are inadequate; (3) altered receptor-antibody interaction due to the presence of truncated HER-2 receptor p95HER-2 with distinct biologic properties in breast cancer cells or to the presence of membrane associated mucin (MUC4) that might mask HER-2 preventing it from binding to the target protein; (4) modified target regulating proteins such as the absence of the phosphatase and tensin homolog (PTEN) that increases PI3K/Akt signaling, the lack of cMyc, the downregulation of the cyclin-dependent kinase—nhibiting protein p27; (5) alternative pathway signaling through insulin-like growth factor 1 receptor (IGF1R) or other HER receptor. A better comprehension of them is a challenge for oncologists.

In the attempt to overcome trastuzumab resistance, several trials are ongoing with novel biological agents alone or combined with trastuzumab. ■

A version of this article containing references can be found in the Reference Section on the website supporting this briefing (www.touchoncology.com).