

# HER2-positive breast cancer, how far away from the cure?—on the current situation of anti-HER2 therapy in breast cancer treatment and survival of patients

Ning Liao

Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital, Guangzhou 510080, China

Correspondence to: Professor Ning Liao. Guangdong Provincial People's Hospital, Guangzhou 510080, China. Email: drliao\_ning@hotmail.com.

**Abstract:** With the diagnosis and treatment of tumor enter into the area of precision medical, based on selected targeted molecular typing of patients with individualized diagnosis and treatment play an important role. HER gene encoded epidermal growth factor receptor 2 (HER2) leading to increased early distant metastasis of breast cancer in patients and poor prognosis. However, a number of clinical studies provided evidence-based anti-HER2 targeted therapy and confirmed the benefit of anti-HER2 targeted therapy in patient survival. In recent years, through the tireless efforts of scholars in the field of breast cancer in our country, the whole diagnosis and treatment of breast cancer has accomplished an international standard. But based on a variety of factors, the anti-HER2 targeted therapy between China and the developed countries, and between different areas in China still exists certain gaps, is now a problem need to be solved. This article will analyzing the diagnostic and treatment on HER2-positive breast cancer in the United States and China, exploring reasons and looking for answers to narrow down the gap in the treatment of HER2-positive breast cancer between China and the United States. Improve the anti-HER2 targeted therapy in our country, let the patients get maximum benefit from anti-HER2 targeted therapy.

**Keywords:** Breast cancer; epidermal growth factor receptor 2 (HER2); targeted therapy; diagnosis and treatment status; standard treatment

Submitted Apr 10, 2016. Accepted for publication May 22, 2016.

doi: 10.21037/cco.2016.05.10

View this article at: <http://dx.doi.org/10.21037/cco.2016.05.10>

## The course of epidermal growth factor receptor 2 (HER2)-positive breast cancer treatment from clinical trials to clinical practice

Breast cancer is one of malignant tumors affecting women's health. The Global Cancer Statistics (GLOBLCAN) published in February 2015 showed that there were around 1.67 million women suffering from breast cancer, more than 500,000 patients died of breast cancer, and the incidence and mortality all ranked first among cancers in women (1). According to the latest published data on cancer incidence and mortality by our National Cancer Center, the number of cases of breast cancer ranks first in female cancers, while the number of deaths of women with breast cancer ranks only sixth (2), indicating preliminarily, that, through the tireless efforts of scholars in the field of breast cancer for

decades, our breast cancer treatment has accomplished an international standard.

Breast cancer is a systemic disease, and molecular diagnostics plays an increasingly important role in breast cancer diagnosis and treatment in individualized clinical practice. Based on selected targeted molecular typing of patients, endocrine therapy of breast cancer has become standards in individualized treatment. HER gene encoded HER2 is a transmembrane tyrosine kinase receptor, the activation of which can promote sustained proliferation of breast cancer cells, leading to increased degree of malignancy in the biological behavior of tumor cells, early distant metastasis of breast cancer in patients, and poor prognosis. According to previous research data, HER2-positive breast cancer

accounts for about 20% to 25% of all breast cancer patients (3-6).

Trastuzumab is the first humanized monoclonal anti-HER2 antibody approved by the US Food and Drug Administration (FDA) in 1998 for targeted therapy. In the last two decades, with its increasingly widespread clinical application, clinical outcomes in patients with HER2-positive breast cancer have been improved significantly. A number of major international clinical studies have confirmed the benefit of trastuzumab in patient survival (7-9). Treatment guidelines with high international impact, such as guidelines of the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), all included the anti-HER2 therapy as the recommended diagnosis and treatment for HER2-positive breast cancer, clearly pointing out that trastuzumab is the cornerstone in the adjuvant therapy for HER2-positive breast cancer.

In recent years, our scholars in the field of breast cancer are constantly learning to absorb and accumulate experiences and to improve diagnosis and treatment in the anti-HER2 therapeutic area. While committed to optimizing the breast cancer diagnosis and treatment strategy and improving the survival of patients with breast cancer, there are still some gaps in clinical standard among areas. What aspects are exactly in the gaps? How big are the gaps? Clinical researchers need to trace the origin and expand the thinking to continually narrow down the gap between China and European and American countries as well as between our different areas to improve the diagnosis and treatment of breast cancer and to maximize the survival benefit for breast cancer patients.

Thus, at the 10th Shanghai International Forum on Breast Cancer recently organized by the Chinese Anti-Cancer Association Breast Cancer Committee (CBCS), Fudan University Cancer Hospital, and the Shanghai Cancer Institute, experts and scholars in the field of breast cancer from China and the United States had an discussion and exploration on the current status of HER2-positive breast cancer treatment to promote the development of anti-HER2 targeted therapy.

### **Knowing each other: the diagnostic and treatment on HER2-positive breast cancer in the United States and China**

#### *USA anti-HER2 therapy report*

Professor Ian Krop from the Harvard Medical School

Dana-Farber Cancer Institute presented the investigation data on HER2-positive breast cancer in recent years in America.

A study published in the *Journal of Clinical Oncology* in 2015 showed that, when comparing the risk of recurrence in breast cancer patients treated from 1986 to 1992 and from 2004 to 2008, with the gradual adoption of anti-HER2 therapy, the risk of recurrence in patients with HER2-positive breast cancer has been significantly reduced (10). There are also a number of clinical studies confirming that anti-HER2 targeted therapy can reduce the risk of recurrence in patients with HER2-positive breast cancer, improving the patient prognosis. Therefore, with further optimization of HER2 therapeutic strategies, the current US standard adjuvant anti-HER2 treatment is: the treatment duration is one year as the best in most cases; treatment regimen can choose trastuzumab in a combination therapy, or superior in a sequential treatment.

Although trastuzumab has been shown to significantly improve the HER2 positive early breast cancer survival, what is the practical application of anti-HER2 targeted therapy in the USA?

NCCN, composed of 25 major college cancer centers located in different cities of the USA, prospectively collects clinical data in order to conduct related research. There is one collection on the rate of anti-HER2 targeted therapies on HER2-positive breast cancer patients in the USA. The study included 1,109 cases of stages I to III HER2-positive breast cancer data from eight NCCN institutions from September 2005 to December 2008. The results showed that 83% of the overall population of patients received trastuzumab treatment. In subgroup analysis, comparing the trastuzumab usage in patients of different ages, the proportion of patients receiving and completing trastuzumab treatment was significantly lower in patients aged 70 years and older ( $P < 0.0001$  and  $P = 0.022$ , respectively). Comparing the trastuzumab usage in breast cancer patients with other diseases, the group of patients with two or more other diseases had a lower proportion in receiving trastuzumab treatment ( $P = 0.0008$ ). Comparing the trastuzumab usage in breast cancer patients of different races and education levels, the proportion of patients completing trastuzumab treatment was lower in the black population and in patients with a lower level of education ( $P = 0.007$  and  $P = 0.006$ , respectively).

In a study published in *Cancer* in 2013 (11), researchers pointed out that ensuring the trastuzumab usage and

analyzing the factors hindering the usage of targeted therapy are very necessary in order to be able to guarantee the standard treatment of HER2-positive breast cancer and to improve patient outcomes.

A study published this year in *Journal of Oncology Practice* (12), is about data from the “real world”. The study is a retrospective analysis of the treatment regimen and cost of 915 cases of American HER2 positive early breast cancer patients from the private health insurance claims data. It included patients diagnosed of stage I to III breast cancer from January 2008 to August 2013. The results showed that a total of 657 cases received anti-HER2 targeted therapy in the general population of patients (72%). In the neoadjuvant therapy, 47% of the patients received the carboplatin + docetaxel + trastuzumab program. In the adjuvant therapy, 30% of the patients received the carboplatin + docetaxel + trastuzumab ± endocrine therapy.

## Current HER2 detection and treatment of breast cancer patients in China

### *Progress of HER2 detection in China*

Anti-HER2 targeted therapy progressed gradually since the approval of trastuzumab in China in 2002. The primary criterion on whether to use the anti-HER2 therapy is the test result of HER2 levels. To further promote the standardization of HER2 testing in breast cancer, China issued the “Breast cancer HER2 testing guidelines” in 2009, and updated and supplemented it in 2014 (13). Meanwhile, the National Health and Family Planning Commission established a HER2 testing quality control program in 2010, and as of 2015, the program has covered 289 centers nationwide. HER2 breast cancer detection rate in China has been significantly improved, rising from 57% in 2008 to 86% in 2011.

### *Current status of anti-HER2 therapy*

Professor Guangyu Liu, Fudan University Cancer Hospital, has pointed out that, there is a lack of large-scale data on our anti-HER2 treatment of HER2-positive breast cancer patients. A 2011 study published in the *Journal of Cancer Research China* reported data on the anti-HER2 therapy for HER2-positive breast cancer patients in the Beijing area in 2008 (14); the results showed that only 20% HER2-positive patients received a targeted therapy. A 2014 study published in the *Lancet Oncology* also showed that, in spite

of trastuzumab being listed in China in 2002, only 20.6% of HER2-positive breast cancer patients received the anti-HER2 therapy in Beijing (15).

To further understand the current status of anti-HER2 therapy in breast cancer patients and fight for the benefit of survival for patients, CBCS launched a large-scale survey named the “Goddess Project (CBCSG029)” (learned from report by Prof. Liu Guangyu in SIBCS 2015). The study carried out a nationwide survey on the rate of adjuvant anti-HER2 targeted therapy for HER2-positive breast cancer patients, including summary analysis of the rate of targeted treatment to factors of patient age, TNM stage, and hormone receptor expression.

As of September 30, 2015, the Goddess Project covered 29 provinces, municipalities and autonomous regions nationwide with 155 participating hospitals, and reported a total of 4,981 cases of HER2 positive stage I to III breast cancer patients under the selection criteria from July 1, 2013 to December 31, 2013, in which the number of patients in Guangdong, Henan, Jiangsu, Liaoning, Shandong, Sichuan and Shanghai exceeded 300 cases.

The results showed that in the overall population, the rate of adjuvant anti-HER2 targeted therapy was 34.31%, and neoadjuvant anti-HER2 targeted therapy was 18.6%, suggesting that the targeted therapy was not sufficient in the HER2 positive early breast cancer treatment in China. In terms of geographical analysis, there were differences in the rate of anti-HER2 targeted therapy, with higher rates of target therapy in Beijing (64%), Guangdong (51%), Shanghai (43%), Jiangsu (58%) and Zhejiang (43%). Analysis of factors related to HER2 targeted therapy shows that different adjuvant chemotherapy, the patient's age and hormone receptor status have no significant effect on HER2 targeted therapy. Among factors affecting the targeted therapy in a multi-factor analysis, the locality of patients ( $P<0.001$ ), lymph node status ( $P<0.001$ ) and primary tumor stage ( $P=0.003$ ) in patients are related to the anti-HER2 target therapy, potentially affecting the usage of targeted treatment (unpublished).

In summary, the detection coverage of HER2 status in breast cancer and the extent of regulation has greatly improved in China. In the treatment, there is an increase in the proportion of HER2-positive breast cancer treated with anti-HER2 targeted therapy, but it has wide regional differences and the overall proportion of HER2-positive patients receiving anti-HER2 targeted therapy is still not high, especially in patients with early stages of breast cancer.

### The details: in depth analysis of the impact of anti-HER2 therapy on the survival of breast cancer patients

Research data set forth above has illustrated the current status of anti-HER2 therapy in China and in the USA. Will the adoption of targeted therapy for HER2-positive breast cancer affect the survival of patients, and if so, how much is the impact? We will look for answers through clinical data and analysis on real-world treatment conditions.

#### *A number of clinical studies provided evidence-based anti-HER2 therapy*

Since the development and usage of trastuzumab, the international field of breast cancer study has carried out a number of large scale classic adjuvant therapy in clinical studies, including NSABP B-31, NCCTG9831, HERA, FinHer and BCIRG006, etc. (8,15-17), all having explored the efficacy, the treatment time and the best treatment modality using trastuzumab in HER2-positive breast cancer patients. The results of these studies have subsequently confirmed that the adoption of trastuzumab for HER2-positive breast cancer can reduce the risk of recurrence of early breast cancer by about 50% and lower the risk of death by about 30%.

N9831 and NSABP B-31 studies have compared the adjuvant treatment efficacy in HER2-positive breast cancer patients with AC-T program (anthracycline plus cyclophosphamide sequential paclitaxel) with or without trastuzumab, jointly analysing the patient overall survival (OS) and disease-free survival (DFS). The results showed that the DFS rate of patients with trastuzumab had significantly improved over the group of patients without trastuzumab treatment [73.7% vs. 62.2%, hazard ratio (HR) of 0.6,  $P < 0.001$ ], the OS rate was also significantly increased (84% vs. 75.2%, HR was 0.63,  $P < 0.001$ ). The cumulative incidences of distant metastasis (first event) in the trastuzumab usage group had an absolute reduction of 9.6%.

Not only in the adjuvant treatment stage, the NOAH study of neoadjuvant therapy using trastuzumab has confirmed that anti-HER2 targeted therapy significantly improved the neoadjuvant therapy for patients with complete pathological remission (9). Another study published in the “*Journal of Clinical Oncology*” (JCO) from the United States M.D. Anderson Cancer Center, included 2,091 cases of patients with HER2-positive advanced breast cancer, and proved that the prognosis can be improved

in patients with advanced breast cancer by the usage of trastuzumab (7).

#### *Reality check: answers to the impact of survival by our specific data*

Because trastuzumab is late into the market in China, and its usage is limited by socio-economic factors, about 80% of HER2-positive patients are unable to receive the anti-HER2 targeted therapy. There is relatively a lack of clinical data on patient usage of trastuzumab, and no published data analyzing the benefit on patient survival in China.

Recently, the breast surgery team at the Cancer Center of Guangdong Provincial People’s Hospital conducted a retrospective study on their HER2-positive breast cancer patients, statistically analyzing the clinical application of trastuzumab in postoperative adjuvant therapy and patient survival data in order to obtain the clinical information and to guide the treatment in China.

The study has gathered 286 treated cases of stage I to III patients with HER2-positive breast cancer from January 2005 to August 2015, with a median age of 49 years, of which 72 cases were at stage I, 162 cases at stage II, and 52 cases at stage III, covering data on the anti-HER2 targeted patient treatment, DFS and OS.

The results showed that all patients received guideline-recommended standard adjuvant therapy, including hormonal therapy or radiotherapy. The adjuvant trastuzumab treatment were sufficient (defined as assisted trastuzumab  $\geq 1$  year) in 143 patients (50%), insufficient (defined as assisted trastuzumab treatment  $\geq 9$  weeks and  $< 1$  year) in 22 patients (7.7%), almost unused or never used (defined as trastuzumab treatment  $< 9$  weeks or never used) in 121 patients (42.3%).

Survival analysis showed that the 5-year DFS rate for the three groups of patients was 92.4%, 62.0% and 72.1%, respectively. The DFS rate in the trastuzumab treatment group of at least 1-year was significantly superior to the insufficient treatment group ( $P < 0.001$ ) and the treatment of less than 9 weeks or never used group ( $P < 0.001$ ).

Similar to the DFS survival results, the 5-year OS of the three subgroups was 96.0%, 81.0% and 80.0%, respectively. The OS rate in the trastuzumab treatment group of at least 1-year was significantly better than the insufficient treatment group ( $P = 0.022$ ) and the treatment of less than 9 weeks or never used group ( $P < 0.001$ ).

The COX regression analysis including the age, clinical stage, adjuvant trastuzumab treatment time,

Ki-67 index, and molecular subtype revealed that the adjuvant trastuzumab treatment time was an independent predictor for DFS and OS ( $P < 0.05$ ). The at least 1 year of trastuzumab adjuvant therapy can reduce the risk of recurrence in HER2-positive patients by approximately 80% (HR = 0.207,  $P < 0.0001$ ) and the risk of death by 78% (HR = 0.218,  $P < 0.002$ ).

The retrospective study by our Cancer Center has provided data on the Herceptin clinical application in HER2-positive breast cancer in the Chinese population. The application of trastuzumab targeted therapy for HER2-positive breast cancer patients in the Center was 57.7% in the past 10 years, while in the previously mentioned survey data in the Goddess Project, rate of targeted therapy at this Center was as high as 85%, much greater than the rate in other regions. With the progress of socio-economic factors, the rate is being further improved in recent years. In the foreseeable future, the prognosis of HER2-positive patients will be further improved with expanded application of the targeted treatment.

The study also provided sound data on the survival analysis comparable to the Western population. The up to 80% reduction in the risk of recurrence and mortality, once again, prompted the need for sufficient course of at least 1 year of trastuzumab for HER2-positive breast cancer to improve the prognosis in the Chinese population.

### **Exploring reasons and looking for answers to narrow down the gap in the treatment of HER2-positive breast cancer between China and the USA**

#### *Pursuing the causes for fundamental improvement*

First, the economic factors.

- (I) Patient's inability to pay leads to a reduced rate of the targeted therapy: although our national economy has been steadily improving, there is still a certain gap with developed countries. The advantages of good efficacy and safety of targeted therapies comes with the inevitable disadvantage of expensively patented drugs. In addition, the improved diagnosis and treatment of breast cancer has greatly increased the OS of patients, which extends the treatment cycle and adds to the treatment cost. These factors have burdened HER2-positive breast cancer patients with a heavy financial cost unable to afford the targeted therapy

after a definite diagnosis. But in recent years, under the appeal of domestic scholars and the cooperation of pharmaceutical companies, there have developed a trastuzumab charitable program donating the medicine, which has to a certain extent lessened drug-related burden for the treatment of breast cancer patients;

- (II) Effects of medical insurance policies on pharmaceutical applications: data in the Goddess Project showed that before June 2014 when provinces and cities in our country, Jiangsu, Guangzhou, and Qingdao, included trastuzumab in the medical insurance, the proportion of targeted therapy was 62.63% in cities covered with the medical insurance, while it was only 29.18% in cities not covered with the insurance. In the aforementioned retrospective study at Guangdong Provincial People's Hospital, the influence of medical insurance policies on the choice of adjuvant targeted therapy for stage I to III HER2-positive breast cancer patients was also analyzed in addition to the analysis of survival and prognosis. Results of the study showed that for patients with or without the insurance, rate of the targeted therapy application was 33.1% or 17.5%, respectively, revealing the potential influence of medical insurance on the choice of targeted treatment. Overall, our indicators of the availability, feasibility and affordability of targeted medicine are not up to the level in developed countries and regions, awfully limiting the clinical treatment of breast cancer patients in our country. Therefore, it requires the collective wisdom of the government, pharmaceutical companies and the medical system to achieve the accessibility of targeted drugs in cancer patients, and to maximize its therapeutic value so that more patients will benefit.

Second, the standardized treatment.

In addition to economic factors, the clinician's treatment concept is bound to have some impact on the use of targeted drugs. Targeted therapy, as a safe and effective anti-tumor treatment, by virtue of its advantages, plays an increasingly important role in tumor treatment. It has become the choice for cancer treatment as important as surgery, radiotherapy and chemotherapy; cancer treatment can be described as entering the period of targeted therapies.

Currently, many clinicians in first-tier cities have accepted the concept of targeted therapy. But relatively big gaps can still be found when comparing data on the

proportion of targeted therapy in different provinces, or in different cities in a province. For example, in Guangdong province, statistical data on the rate of targeted therapy for HER2-positive breast cancer patients has revealed occurrences of 0% in some hospitals. Therefore, the advantages of targeted therapy and its importance in the overall treatment of breast cancer need to be emphasized, and the regular requirement of targeted therapy needs to be standardized to avoid any adverse effect on the patient survival as a result of poor treatment concept.

### Summary

It was not difficult to find out that using the targeted therapy or not will exert a profound effect on the survival of HER2-positive breast cancer patients, as revealed in the above research on data and practical treatment. The USA current survey data shows that the rate of targeted therapy in patients with HER2-positive patients is as high as 70% to 80%, while our rate of targeted therapy on HER2-positive breast cancer patients is only about 30%, indicating that the availability of trastuzumab anti-HER2 targeted therapy in our country has a large lag behind the USA and other developed countries. The lower usage of targeted therapy is seriously related to a follow-up relapse of breast cancer, inevitably resulting in a heavy health burden. Therefore, urgent attention is needed on targeted therapy of HER2-positive breast cancer patients, for a fundamental solution to various problems, for a timely and sufficient anti-HER2 therapy application, and for improving the rate of targeted therapy and the prognosis of breast cancer patients in China.

### Acknowledgements

*Funding:* This research was supported by a grant encoded as S2012A030400016 from Guangdong Province Technology Program.

### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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**Cite this article as:** Liao N. HER2-positive breast cancer, how far away from the cure?—on the current situation of anti-HER2 therapy in breast cancer treatment and survival of patients. *Chin Clin Oncol* 2016;5(3):41. doi: 10.21037/cco.2016.05.10