Chinese-German J Clin Oncol
DOI 10.1007/s10330-314-0015-7
December 2014, Vol. 13, No. 12, P555–P559

Efficiency and safety of trastuzumab plus chemotherapy in Her-2 overexpressing metastatic breast cancer patients*

Jianfei Guo[1], Zhaozhe Liu (Co-first author)[1], Guojing Zhang[1], Tao Han[1], Fang Guo[1], Yaling Han[2], Xiaodong Xie (✉) [1]

[1] Department of Oncology, The General Hospital of Shenyang Military, Shenyang 110016, China
[2] Cardiovascular Disease Institute, The General Hospital of Shenyang Military, Shenyang 110016, China

Received: 20 October 2014 / Revised: 5 November 2014 / Accepted: 20 November 2014

Abstract ***Objective:*** The aim of this study was to evaluate the safety and efficiency of combination of trastuzumab and chemotherapy as first line regimen in Her-2 overexpressing metastatic breast cancer (MBC) patients. The primary endpoint was overall response rate (ORR) and the second endpoint was clinical benefit rate (CBR) and toxcities. ***Methods:*** Estrogen receptor (ER) (–), progesterone receptor (PR) (–), Her-2 (+++) patients were included in the study. 126 eligible patients were divided into 2 groups, 51 of them were assigned to the Herceptin group (H group) and 75 of them were assigned to the Control group (C group). They were treated by commonly used chemotherapy regimens with or without trastuzumab. ***Results:*** Response rate (RR) of the H group and the C group were 51.0% and 24.0% separately, and the difference were statistically significant ($P < 0.05$). CBR of the two groups were 76.4% (H group) and 64.0% (C group), had significant difference ($P < 0.05$). Complete response rate (CRR) of the two groups were 21.5% and 6.6%, there were no significant difference between the two groups ($P = 0.055$). Grade 3–4 cardiac toxicity were recorded in 9 patients with trastuzumab plus chemotherapy (17.6%) and 4 patients with chemotherapy (5.4%), with no statistical significance ($P = 0.054$). In the subgroup of antharcycline-containing regimens, Grade 1–4 cardiac toxicity occurred in 9 patients in the trasutuzumab combining with antharcycline-containing regimens arm [herceptin plus anthracycline contained chemotherapy (H + ACCT arm; 40.9%, 9/22)], and 4 patients in the antharcycline-containing chemotherapy arm (ACCT arm; 12.5%, 4/32). There was statistical significant difference between the two arms ($P < 0.05$). Grade 3–4 cardiac toxicity, the occurance rates were 18.1% (4/22) in H + ACCT arm and 6.3% (2/32) in ACCT arm, and there was no significant statistical difference ($P = 0.352$). Grade 3–4 granulocytopenia in the H group and C group were 27.5% (14/51) and 26.7% (20/75), with no significant difference ($P = 0.922$). ***Conclusion:*** The efficiency of trastuzumab combining with chemotherapy using as first line regimen in Her-2 overexpressing MBC patients were exact. However, the long-term cardiac toxicity can be hidden troubles of trastuzumab using.

Key words herceptin; metastatic breast cancer; first-line chemotherapy

Breast cancer, which occurance rate takes a lead in China for a long time, is also one of the most common malignancies that threats women health worldwide. The expression status of human epidermal growth factor 2 (Her-2/c-erbB2)plays a vital role in the choices of breast cancer therapies [1]. The Her-2 overexpressing breast cancer [2], about 17 percent of breast cancer, has the characteristics of high malignant degree, poor prognosis, a larger frequency of drug resistant and affecting the disease free survival rate notably on account of its unique pathological pattern: estrogen receptor (ER) negative, progesterone receptor (PR) negative, Her-2 positive. Many evidences showed the remarkable curative effect promotion in the combination of trastuzumab with chemotherapy applying as the first line regimen in Her-2 ovexpression metastatic breast cancer (MBC) patients in recent years, which caused a widespread use of trastuzumab [3]. Nevertheless, a recent systemic review [4] found out that although trastuzumab improved overall survival (OS) and progression-free survival (PFS) in Her-2 positive women with MBC, but it also increased the risk of cardiac toxicities, such as congestive heart failure and left ventricular ejection fraction decline, and a long-term increased risk of metastasis to the central nervous system also couldn't be neglected. What's more, in their research,the recruitment in three

Correspondence to: Xiaodong Xie. Email: doctor_xxd@163.com
* Supported by grants from the Sub-topics of Major Drug Discovery Platform in the Twelfth-Five Year Research Program of China (No. 2012ZX09303016-002) and Liaoning Province Science & Technology Development Funds (No. 2012225019).

out of seven studies was stopped early and in three trials more than 50% of patients in the control groups were permitted to switch to the trastuzumab arms at progression, making it more difficult to understand the real net benefit of trastuzumab.

We enrolled 126 MBC patients treated in our department, aiming to evaluate the efficiency and safety of trastuzumab plus first line chemotherapy, compared with chemotherapy without targeted therapy in women with Her-2 overexpressing MBC patients.

Materials and methods

Information

General information

We enrolled 126 patients treated in our department between January 2006 and March 2014. All of them were verified as ER (–), PR (–), Her-2 positive [3 + immunohistochemistry, or a positive score by fluorescence in situ hybridization (FISH)]. The age of eligible patients varied from 37 years old and 65 years old, whose mean age was 52.42, 70 of them were postmenopausal, 56 of them were premenopausal. All of the patients had normal blood routine and hepatic and renal function, normal electrocardiography, normal cardiac function, ≥ 50% left ventricular fraction, and 0–2 points according to Eastern Cooperative Oncology Group performance status. They were all Stage IV patients according to international unifying new TNM classification. Eligible patients were all postoperative after regular adjuvant chemotherapy and found progression afterwards. They all were diagnosed and treated initially in our department when found progression. As for the metastatic sites, 67 of them had bone metastases, 25 of them had lung metastases, 14 of them had liver metastases, 45 of them had local progression such as axillary, subclavicular, cervical lymph nodes and chest wall. There were 19 of them had double metastatic sites and 3 of them had triple ones (Table 1).

Grouping

The 126 eligible patients were divided into 2 groups, 56 of them were assigned to the Herceptin group (H group) and 70 of them were assigned to the Control group (C group). There were no significance in age menopausal status and metastatic sites between the two groups, therefore, they were comparative.

Standard of efficiency

Tumor response data (RR) were assessed by investigator according to the Response Evaluation Criteria in solid tumors 1.1. Complete response (CR): disappearance of all target lesions; partial response (PR): at least a 30% decrease in the sum of diameters of target lesions; Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions; stable disease(SD): neither shrinkage to qualify for PR nor sufficient increase to qualify for PD. RR = PR rate (PRR) + CR rate (CRR). Clinical benefit rate (CBR) = CRR + PRR + SD rate (SDR). The toxicity was evaluated according to toxic grading standard NCI-CT 3.0.

Table 1 General clinical information and subgroups (*n*)

Characteristics	H group	C group	Total
Enrolled amounts	51	75	126
Mean age (years)	56.07	50.00	52.42
Menopausal status			
Premenopausal	21	35	56
Postmenopausal	33	37	70
Immunohistochemistry results	ER (–)	PR (–)	Her-2 (+++)
TNM stages in all groups			
Metastatic sites			
Bone	27	40	67
Lung	13	12	25
Liver	6	8	14
Local sites (lymph & chest wall)	18	27	45
Chemotherapy regimens			
DX	21	22	43
DE	16	24	40
CE	6	8	14
GC	5	13	18
CMF	2	6	8
Docetaxel	0	2	2
Xeloda	1	0	1
Response			
CR	11	5	16
PR	15	13	28
SD	13	30	43
PD	12	27	39

Therapies

H group

Docetaxel + xeloda (DE) + H: trastuzumab 8 mg/kg first time, 6 mg/kg afterwards VD continuously plus docetaxel (Doc) 60–75 mg/m^2 d1, epirubcin (EPI) 25–32.5 mg/m^2 d1–2, 21d/cycle. Cytoxan + epirubicin (CE) + H: trastuzumab 8 mg/kg first time, 6 mg/kg afterwards VD continuously plus cyclophosphamide (CTX), 450–600 mg/m^2 VD d1, EPI 25–32.5 mg/m^2 d1–2, 21d/cycle. Docetaxel + xeloda (DX) + H: trastuzumab 8 mg/kg first time, 6 mg/kg afterwards VD coutinuously plus Doc 60–75 mg/m^2, capecitabine (Cap) 950–1250 mg/m^2, po bid, d1–14, 21d/cycle. Gemcitabine + cytoxan (GC) + H: trastuzumab 8 mg/kg first time, 6 mg/kg afterwards VD continuously plus CTX 450–600 mg/m^2 VD d1, gemcitabine (GEM) 900–1250 mg/m^2, VD d1, d8, 21d/cycle. Cytoxan+ methotrexate + 5-FU (CMF) + H: trastuzumab 8 mg/kg first time, 6 mg/kg afterwards VD continuously plus CTX 450–600 mg/m^2, VD d1, methotrexate (MTX) VD, d1, d8, 5-FU 500–600 mg/m^2, VD d1, d8, 28d/cycle. X + H: trastuzumab 8 mg/kg first time, 6 mg/kg afterwards VD continuously

plus Cap 950–1250 mg/m^2, po bid, d1–14, 21d/cycle.

C group

DE: Doc 60–75 mg/m^2 d1, EPI 25–32.5 mg/m^2 d1–2, 21d/cycle. CE: CTX, 450–600 mg/m^2 VD d1, EPI 25–32.5 mg/m^2 d1–2, 21d/cycle. DX: Doc 60–75 mg/m^2, d1, Cap 950–1250 mg/m^2, po bid, d1–14, 21d/cycle. GC: CTX 450–600 mg/m^2 VD d1, GEM 900–1250 mg/m^2, VD d1, d8, 21d/cycle. CMF: CTX 450–600 mg/m^2, VD d1, MTX VD, d1, d8, 5-FU 500–600 mg/m^2, VD d1, d8, 28d/cycle. D: Doc 60–75 mg/m^2, d1, 21d/cycle.

Statistical analysis

SPSS 21.0 was applied on the data analysis. Pearson's χ^2 test, continuity correction χ^2 test were employed on analyzing the differences between enumeration data.

Results

Promotion of curative effect in H group

Firstly, the RR of the H group and the C group were 51.0% and 24.0% separately, and the difference were statistically significant ($P < 0.05$).

Secondly, CBR of the two groups were 76.4% (H group) and 66.0% (C group), had significant difference ($P < 0.05$).

However, CRR of the two groups were 21.5% and 6.6%, there were no significant dfference between the two groups ($P = 0.055$; Table 2).

Table 2 Comparison of clinical response

Efficiency	H group (%)	C group (%)	χ^2	*P*
CRR	21.5	6.6	3.690	0.055
ORR	51.0	24.0	9.724	0.002
CBR	76.4	64.0	4.892	0.027

Table 3 Main Adverse effects

Adverse effects	H group (%)	C group (%)	χ^2	*P*
Cardiac toxicity				
Grade III–IV	17.6	5.4	3.706	0.054
In ACCT subgroup				
Grade III–IV	18.1	6.3	0.865	0.352
Grade I–II	40.9	12.5	4.307	0.038
Granulopenia grade III–IV	27.5	26.7	0.009	0.922

Toxicity and safety

Cardiac toxicity

Grade 3-4 cardiac toxicity were recorded in 9 patients with trastuzumab plus chemotherapy (17.6%) and 4 patients with chemotherapy (5.3%), with no statistical significance ($P = 0.054$). In the subgroup of antharcycline-containing regimens, grade 1–4 cardiac toxicity occurred in 9 patients in the trastuzumab combining with anthracycline-containing regimens arm (H + ACCT arm; 40.9%, 9/22), and 4 patients in the antharcycline-containing chemotherapy arm (ACCT arm; 12.5%, 4/32). There was statistical significant difference between the two arms ($P < 0.05$). However, as for grade 3–4 cardiac toxicity, the occurance rates were 18.1% (4/22) in H + ACCT arm and 6.3% (2/32) in ACCT arm, and there was no significant statistical difference ($P = 0.352$; Table 3).

Other adverse events and toxicities

In our study, there was no treatment-related death in all groups. In the H group, fever and chill occurred for using the trastuzumab for the first time in 6 patients, all of them got improvement in symptoms after slowing down the dripping speed and symptomatic treatment. Different grades of myelosupression emerged in patients in all groups. The occurrence rate of 3–4 grade granulocytopenia in the H group and C group were 27.5% (14/51) and 6.3% (2/32), with no significant difference ($P = 0.352$). And all the patients could tolerate with granulocytopenia and could get symptom improved after standard recombinant human granulocyte colony-stimulating factor therapies. Other toxicities and adverse events (AEs) were different of grades of gastrointestinal reaction, liver function damage, dental ulcer, neurotoxicity of periphral nerve, etc. They all could be well tolerated and treated by therapies such as anti-emesis, fluid infusion, liver protection and so on.

Discussion

Efficiency of trastuzumab combine with chemotherapy

Trastuzumab (herceptin), which is a humanized monoclonal antibody aim at Her-2, can inhibit tumor cell growth [5] by inhibiting Her-2 pathway, antibody dependent cell-mediated cytotoxicity and antiangiogenesis is one of the most vital targeted drugs for Her-2 overexpressing breast cancer patients. It had been reported that [6] trastuzumab combined with first line chemotherapy could improve the overall response rate (ORR) from 32 to 50 compared with chemotherapy only regimens. A phase II, multicentre clinical trail by Aogi K indicated that [7], the CRR of trastuzumab plus chemotherapy as first line could reach 19.2%, and the ORR got as high as 67.6%. What's more, there were multiple amounts of studies whose end point were OR [8–10] manifested that by combining with trastuzumab can benefit the MBC patients treated by first line chemotherapy, which were basically consistent with the results of our study. Nevertheless, our study didn't support the point of view that trastuzumab can improve the CRR in Her-2 overexpressing MBC patients.

Does the chemotheray regimens combined with trastuzumab matters?

A phase III clinical trial [11] declared that the efficiency

Table 4 ORR of different chemotherapy regimens

ORR	DE (%)	DX (%)	χ^2	*P*
All groups	35.0	41.9	0.412	0.521
C group	21.7	35.0	0.935	0.334

of trastuzumab plus chemotherapy (doxorubicin, CTX, taxanes) showed better than chemotherapy only, the ORR was 15–26%. Trastuzumab combined with other chemotherapeutics (GEM, vinorelbine) can also showed a ideal efficiency, whose ORR could reach 40%–60% [12–14]. The chemotherapy regimens that were enrolled in our study were all the most commonly used regimens as first line chemotherapy in MBC patients, a great majority of regimens contained taxanes or antharcyclines. The most involved regimens in our research were DX and DE, we compared these two regimens and found that there were no statistical significance between this two arms (P = 0.521). Additionally, there was also no significance between the two regimen in the subgroup of C group (P = 0.334; Table 4).

Trastuzumab-related AEs

A research result showed that the occurrence rate of chronic heart failue using single agent trastuzumab was about 4%–6% [15]. But it comes to 27% high when combining with antharcycline agents. In our study, the occurrence rate of grade 3–4 cardiac toxicity by using trastuzumab plus antharcycline agents reached 19.2%. 2 patients were recorded occurring the symptoms of chest pain and distress, increase of brain natriuretic peptide and was forced withdrawling trastuzumab. In the subgroup of using antharcyclines, grade 1–4 cardiac toxicity occurred in 9 patients in H + ACCT arm (40.9%, 9/22), and 4 patients in the ACCT arm (12.5%, 2/32). There is statistical significant difference between the two arms. However, as for grade 3–4 cardiac toxicity, the occurrence rates were 18.1% (4/22) in H + ACCT arm and 6.3% (2/32) in ACCT arm, and there was no significant statistical difference (P = 0.352). Although grade 1–2 cardiac toxicity didn't affect quality of life and current treatment, it brought some hidden troubles for future maintenance therapies. It was reported that using trastuzumab as maintenance therapy can benefit the patients on condition that first line chemotherapy getting an ideal effect [16]. But if trastuzumab plus antharcyclines were applied as first line therapy, which increases the risks of cardiac toxicity, it means that the risks of unable to tolerate the toxcities during the maintenance therapy will be much higher. What's more, a long-term increased risk of metastasis to the central nervous system is also a hidden trouble for long-term use trastuzumab regimens. These all cast long term using trastuzumab to a further doubt.

In conclusion, the efficiency of trastuzumab combining with chemotherapy using as first line regimen in Her-2 overexpressing MBC patients were exact. However, the long-term cardiac toxicity can be hidden troubles of trastuzumab using, and attention should be paid by clinicians.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Zubeda S, Kaipa PR, Shaik NA, *et al.* Her-2/neu status: a neglected marker of prognostication and management of breast cancer patients in India. Asian Pac J Cancer Prev, 2014, 14: 2231–2235.
2. Kim MJ, Ro JY, Ahn SH, *et al.* Clinicopathologicsignificance of the basal-like subtype of breast cancer: a comparison with hor-mone receptor and HER2/neu-overexpressing phenotypes. Hum Pathol, 2006, 37: 1217–1226.
3. Strauss B. Besthopeorlasthope:accessto phaseIII clinicaltrials of HER2/neu for advanced stage IV breast cancer patients. J Adv Nurs, 2000, 31: 259–266.
4. Balduzzi S1, Mantarro S, D'AmicoR. Trastuzumab-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev, 2014, 6: CD006242.
5. Junttila TT, Akita RW, Parsons K, *et al.* Ligand-independ ent Her-2/Her-3/PI3K complex is disprupted by trastuzumab and is effectively by the PI3K inhibitor GDC-094. Cancer Cell, 2009, 15: 429–440.
6. Slamon D J, Leyland-Jones B, Shak S, *et al.* Use of chemotherapy plus a monoclonal antibody against Her2 for metastatic breast cancer that overexpresses Her-2. N Engl J Med, 2001, 344: 783–792.
7. Aogi K, Saeki T, Ikeda T, *et al.* A multicenter, phase II study of epirubicin/cyclophosphamide followed by docetaxel and concurrent trastuzumab as primary systemic therapy for HER-2 positive advanced breast cancer (the HER2NAT study). Int J Clin Oncol, 2013, 18: 598–606.
8. Tolaney SM, Najita J, Krop IE. *et al*. A phase II study of ixabepilone and trastuzumab for metastatic HER2-positive breast cancer. Ann Oncol, 2013, 24: 1841–1847.
9. Zhou NN, Lin XB, Liu DG, *et al.* Efficacy and toxicity of trastuzumab combined with docetaxel for Her-2/neu overexpressing metastatic breast cancer]. Cancer, 2008, 27: 947–950.
10. Ruiz M, Salvador J, Ladrón A, *et al.* Phase-II study of weekly schedule of trastuzumab, paclitaxel, and carboplatin followed by a week off every 28 days for HER2+ metastatic breast cancer. Cancer Chemother Pharmacol, 2008, 62: 1085–1090.
11. Combleigh, Vogal CL, Trapathy D, *et al,* multinational study of the efficiency and safety of humanized anti-HER2 monoclonal antibody in woman who have HER-2 overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol, 1999, 17, 2639–2648.
12. Papaldo, Fabi A, Ferretti G, *et al.* A phase II study on metastatic breast cancer treated with weekly vinorelbine with or without trastuzumab according to Her2 expression:Changing the natrual history of Her-2 positive disease. Ann Oncol, 2006, 17, 630–636.
13. Burstein HJ, Keshaviah A, Baron AD, *et al.* Trastuzumab plus vinorelbine or taxane chemotherapy for Her2 overexpressiong metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. Cancer, 2007, 110: 965–972.
14. O'shaughnessy JA, Vukelja S, Marsland T, *et al*. Phase II study of

trastuzumab plus gemcitabine in chemotherapy-preatreated patients with metastatic breast cancer. Clin Breast Cancer, 2004, 5, 142–147.
15. Baselga J, Norton L, Albanell J. *et al.* Recombinant humanized anti-Her2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against Her2/nue overexpressing human breast cancer xenografts. Cancer Res, 1998, 58: 2825–2831.
16. Yan M, Lv HM, Zhang MW, *et al.* Maintenance treatment of trastuzumab for patients with advanced breast cancer to achieve long term survival: two case reports and literature review. Chin J Cancer Res (Chinese), 2014, 26: 486–492.

DOI 10.1007/s10330-014-0015-7
Cite this article as: Guo JF, Liu ZZ, Zhang GJ, *er al*. Efficiency and safety of trastuzumab plus chemotherapy in Her-2 overexpressing metastatic breast cancer patients. Chinese-German J Clin Oncol, 2014, 13: 555–559.

Oncology and Translational Medicine
2015年征稿启事

首先，非常感谢国内外广大的读者、作者和肿瘤学专家们对我刊《中德临床肿瘤学杂志（英文）》多年来的大力支持和细心呵护！

经国家新闻出版广电总局批示同意，*The Chinese-German Journal of Clinical Oncology*将于2015年更名为 *Oncology and Translational Medicine*，简称 OTM，中文刊名为《肿瘤学与转化医学（英文）》。*Oncology and Translational Medicine* 仍为中华人民共和国教育部主管，华中科技大学同济医学院主办的医学肿瘤学学术期刊（全英文双月刊），在国内外公开发行。国际、国内刊号为：ISSN 1610-1979（纸质版），1613-9089（网络版）；CN 42-1865/R，邮发代号：38-121。

OTM主要刊载肿瘤学与转化医学相关综述、原创性学术论文，反映国内外肿瘤及肿瘤转化医学领域科研进展和最新研究成果，开展国际学术交流，为提升肿瘤学与转化医学科学研究及临床实践水平服务。辟有述评、专家笔谈、论著、综述、病例报道、短篇报道、人物专栏等栏目。

欢迎国内外肿瘤学医务工作者踊跃投稿、组稿！具体投稿和联系方式请参见杂志版权页。

《肿瘤学与转化医学（英文）》编辑部
2014年12月