DOI: 10.38103/jcmhch.95.2

Original research

CHARACTERISTICS OF HER2-POSITIVE BREAST CANCER, AND THE CURRENT USE OF ANTI-HER2 THERAPY AND ITS RELATED FACTORS

Le Phuoc Thanh¹, Phan Thien Long^{1,3}, Le Ha Tuyet Ny^{1,3}, Tong Ngoc Huong^{1,3}, Tran Khanh Luan², Ho Xuan Dung^{1,3} ¹Hue University of Medicine and Pharmacy ²Hue Central Hospital ³Raising Hope

ABSTRACT

Objective: To describe the characteristics of patients with HER2-positive breast cancer and to identify the proportion of patients using anti-HER2 therapy, and treatment-making related factors.

Methods: An analytical cross-sectional study was conducted on 79 patients with BC and HER2-positive diagnosed by immunohistochemistry (IHC) or with FISH at the Oncology Department of Hue University of Medicine and Pharmacy Hospital and Oncology Center of Hue Central Hospital from 1/2021 to 12/2022. Clinical and pathological features, type of drug, number of cycles using anti-Her2 therapy were recorded using medical documents. The decision-making related factors were recorded by questionnaire interviewing patients and relatives. Exclusion criteria included recurrent or previously treated tumors; having contraindications with anti-HER2 therapy; not being willing to participate in the study. SPSS 22.0 was used for the analysis.

Results: Mean age was 54.14 ± 11.03 . Patients with right-sided BC accounted for 53.1%. 60.8% of tumors were located in the upper right quadrant of the breast. Patient's self-report of lumps was the most common cause of hospitalization (77.2%). By ultrasound, 60.2% of participants had a tumor size of 2 - 5cm. Abnormal lymph nodes were identified in 40.8% of patients. Histopathologically, invasive ductal carcinoma was found in the majority of tumors (75.9%). Stage II was predominant with 59.5% and 7.6% of patients with stage IV. The rate of treatment with Trastuzumab in our study was 27.8%. The main reason that patients refused anti-HER-2 therapy was financial problems (96.5%). The awareness of anti-HER2 therapy among patients and their relatives was significantly associated with the treatment decision (p = 0.007).

Conclusion: Regarding the positive-HER2 BC patients, invasive ductal carcinoma was the major histopathological finding. More than half of the patients were classified as stage II of the disease. The rate of patients undergoing anti-HER2 therapy was 27.8%. Financial problems were found to be the main reason for refusal of treatment. Awareness of anti-HER2 therapy is significantly associated with the patient's decision on treatment.

Keywords: Breast Cancer, HER2, anti-HER2 therapy, Trastuzumab.

I. BACKGROUND

Breast cancer (BC) is becoming a major health problem. According to GLOBOCAN 2020, more than 2 million new BC cases were diagnosed each year, making this disease the most newly diagnosed cancer worldwide [1]. In Vietnam, approximately 60,573 patients are living with breast cancer. It is estimated 124.65 cases per 100,000 habitants [1]. Following the development of molecular histopathology, BC is currently classified into different subgroups. Hormone receptors and Human Epidermal Growth Factor Receptor 2 - (HER2) are

Received: 16/01/2024. Revised: 25/02/2024. Accepted: 16/4/2024. Corresponding author: Ho Xuan Dung. Email: hxdung@huemed-univ.edu.vn. Phone: 0982558945 the major important discoveries, and the latter has an incidence of 15% among BC patients. Abundant evidence showed that HER2-positive BC had an accelerated disease progression and a worse prognosis than the HER2-negative group [2]. The discovery of HER2/neu oncogenic protein has been a game changer for the management of this group. At the time of its FDA approval in 1998, Trastuzumab - a monoclonal antibody that binds to protein HER2- was among the first available targeted chemotherapies and ameliorated outstandingly the current treatment of HER2-positive BC [3]. At the early stage of BC, the efficacy of Trastuzumab as the adjuvant therapy was found to increase the tumor response, disease-free survival, and overall survival of BC with HER2 overexpression [4-6]. A recent meta-analysis of 7 randomized controlled trials over 13864 operable HER2-positive BC patients showed that Trastuzumab combining chemotherapy significantly reduced the tumor recurrence rate and cancer mortality, compared with chemotherapy alone (RR = 0.66 (95%CI: 0.62 - 0.71) and 0,67 (95%CI: 0.61-0.73), respectively [7]. A multicenter cohort study in Sweden in 2022 evaluating the efficacy of Trastuzumab on early-stage BC with positive HER2 expression showed positive results. After a median follow-up of 6.8 years, the Trastuzumab group had a better 5-year survival (93.4%, 95% CI: 91.2-95.6) than the placebo group (87.4%, 95% CI: 82.3-92.0) [8]. Besides monoclonal antibodies, there have been more choices for anti-HER2 therapy including tyrosine kinase inhibitors (TKIs), and antibody-drug conjugates (ADC), which show superior improvement in overall survival and progression-free survival, namely pertuzumab, trastuzumab-deruxtecan, trastuzumab emtansine DM1 (T-DM1), and lapatinib [9]. The first line treatment in HER2-positive metastatic BC patients is now the combination of taxane, trastuzumab, and pertuzumab with a median overall survival of 56.5 months vs. 40.8 months in placebo combination group without pertuzumab (HR = 0.68; 95% CI: 0.56 - 0.84; P < 0.001) [10]. Nevertheless, the anti-HER2 therapy may not apply to all positive-HER2 BC because of its expensive cost. Ample research regarding the use of Trastuzumab was carried out in developed countries. Trastuzumab

was not available for 8 %: when available, 15%-21% reported accessibility only as out-of-pocket expenditure; when not reimbursed, only 10 % of the providers could significantly offer this intervention. Policy solutions are urgently warranted for the selection, prioritization, and reimbursement of essential health interventions, to result in improved population health [11]. Most studies also suggest that trastuzumab may be cost-effective for the treatment of early breast cancer in a 1-year treatment regimen [12]. However, characteristics of patients with HER2 positive BC and the use of anti-HER2 therapy in low-middle income countries remain under-comprehended. Therefore, we conducted the study to describe the characteristics of patients with HER2-positive breast cancer and to identify the proportion of patients using anti-HER2 therapy, and treatment-making related factors.

II. MATERIALS AND METHOD

2.1. Participants

A cross-sectional study on 79 breast cancer patients with HER2-positive status based on immunohistochemical staining or combined with FISH at the Oncology Department of Hue University Hospital and Oncology Center of Hue Central Hospital from January 2021 to December 2022.

Inclusion Criteria: Breast cancer patients histopathologically diagnosed with HER2-positive breast cancer. HER-2 amplification was defined by HER2 immunohistochemical staining with HER2 (+++) (strong staining in >10% of invasive tumor cells) or HER-2 ++ and FISH positive; patients were indicated for adjuvant/neoadjuvant/palliative systemic therapy.

Exclusion Criteria: patients with recurrent or previously treated breast cancer; patients with contraindications to Anti-HER2 therapy; patients who refused to participate in the study.

2.2. Methods

Subject recruitment was convenience sampling. For each participant, demographic characteristics, clinical features and relevant laboratory tests were recorded using the medical records. HER2 evaluation was based on the ASCO/CAP 2013 guidelines, in which the HER2 staining was classified into four levels (0, 1+, 2+, 3+) [13]. Level 2+ (equivocal) indicates incomplete and/

or weak staining, averaging in >10% of invasive tumor cells, or complete and strong staining in <10% of invasive tumor cells. Level 3+ (positive) indicates complete and strong staining in >10% of invasive tumor cells and is easily accessible under low-power microscopy. Following the immunohistochemical staining result, only a result of 3+ was considered HER2-positive. Among patients assigned to anti-HER2 therapy, the type of regimen and financial source for the treatment were surveyed, while patients refusing this therapy were interviewed for the reason with multiple choice questions. To evaluate factors influencing treatment decisions, we use a questionnaire survey interviewing patients or their family members, covering basic aspects of targeted therapy. The knowledge of anti-HER2 therapy was evaluated after the consultation with oncologists. Patients were classified based on the number of correct answers: 'Sufficient': 3/3, 'Normal': 1/3-2/3, or 'Unknown': 0/3. Statistical analysis was performed using SPSS 22.0.

III. RESULTS

3.1. Demographic and medical profile

From January 2021 to December 2022, a total of seventy-nine patients met the inclusion criteria with ages ranging from 28 to 79 years old (mean age: 54.14 ± 11.033). The overall characteristics of the patients are summarized in Table 1 below.

Characteristics	Number (N=79)	Percentage (%)	Characteristics	Number (N=79)	Percentage (%)
Age	54.14 ± 11.033		Axillary Lymph Nodes		
< 40	6	7.6	Present	38	48.1
40 - 49	18	22.8	Absent	41	51.9
50 - 59	31	39.2	Echo		
> 60	24	30.4	Calcification	24	30.4
Clinical symptoms			No Calcification	55	69.6
New-Onset Breast Pain	15	18.9	Invasion		
Nipple Discharge	1	1.2	Non-invasion	30	38.0
Breast Skin Deformation and Contraction	5	6.3	Peritumoral breast tissue	37	46.8
Color Changes in Breast Skin	5	6.3	Adipose tissue	7	8.9
Nipple Retraction	5	6.3	Chest muscle	5	6.3
Orange Peel Texture of the Breast Skin	2	2.5	Mammography		
Breast Skin Ulceration	2	2.5	BIRADS 3	1	3.6
Location			BIRADS 4	10	35.7
Outer Upper Quadrant	48	60.8	BIRADS 5	17	60.7
Inner Upper Quadrant	19	24.0	Stage		

 Table 1: Patient Overall Characteristics

Characteristics	Number (N=79)	Percentage (%)	Characteristics	Number (N=79)	Percentage (%)
Outer Lower Quadrant	9	11.4	Ι	2	2.5
Inner Lower Quadrant	3	3.8	II	47	59.5
			III	24	30.4
			IV	6	7.6

Table 1 provided an overview of patient and tumor characteristics. The majority of patients were over 50 years old. The most common presenting symptom was new-onset breast pain (18.9%), while other symptoms were rare. The tumor location was predominantly in the outer upper quadrant (60.8%). Abnormal axillary lymph nodes were detected in 38 out of 79 subjects on ultrasound, and 30.4% showed calcifications on imaging. Of 28 patients taking mammography, BIRADS 4 and 5 accounted for 35.7% and 60.7%, respectively. The most common observed stages were Stage II (59.5%) and Stage III (30.4%).

3.2. Histopathology and Immunohistochemistry characteristics

The histopathology and IHC results were obtained and classified. There were 79 cases with HER 2 (3+) in our study, we reported no cases with HER2 ++ and FISH +.

Characteristics	Number (N=79)	Percentage (%)	Characteristics	Number (N=79)	Percentage (%)
Histological Subtypes (N=79)			Number of axillary lymph node metastases (N=73)		
Invasive ductal carcinoma	60	75.9	0	39	53.4
Invasive lobular carcinoma	3	3.8	1-3	23	31.5
Mucinous carcinoma	1	1.3	4-9	6	8.2
Papillary carcinoma	1	1.3	≥ 10	5	6.9
Metaplastic carcinoma	1	1.3	IHC		
Other	13	16.4	ER (+)	16	20.3
Histological grade (N=79)			PR (+)	18	22.8
Grade II	41	51.8	HER2		
Grade III	19	24.1	HER2 3+	79	100
Ungraded	19	24.1	HER2 2+ và FISH +	0	0
			Ki-67		
			Ki-67 (-)	0	0
			Ki-67 (+) ≤ 20%	29	36.7
			Ki-67 (+) > 20%	50	63.3

Table 2: Histopathology and Immunohistochemistry characteristics

Invasive ductal carcinoma was the most common histological subtype with 75.9%, and histological grade II was observed in 51.8% of patients in this study. The expression of Estrogen Receptor (ER) and Progesterone Receptor (PR) was found in 20.3% and 22.8% of patients with positive HER2, respectively. There were 63.3% of patients with high expression of Ki-67.

3.3. The treatment decision-making and related factors



Figure 1: The proportion of patients assigned to anti-HER2 therapy

Drug	Number (n) (N=22)	Percentage (%)	
Trastuzumab	21	95.5%	
Trastuzumab plus Pertuzumab	1	4.5%	

Table 3:	The	choice	of anti-	HER2	therap	ŊУ
----------	-----	--------	----------	------	--------	----

Among the 79 patients, 22 patients received HER2-targeted therapy. Most patients were treated with single-agent anti-HER-2 (Trastuzumab) accounting for 95.5% (21/22 patients). One patient received combination therapy with Trastuzumab and Pertuzumab.



Figure 2: Reasons for the refusal of anti-HER2 therapy

Of 57 patients declined targeted anti-HER2 therapy, the financial difficulties and lack of treatment affordability (accounting for 96.5%) was the major reason. Among 22 patients receiving HER2 therapy, 100% of them were supported by health insurance with 60%-of-cost coverage.

Financial sources for anti-HER2 therap

Treatment payment	Number (n) (N=22)	Percentage (%)
Self-payment	1	4.5
Family contribution	15	68.2
Social relationships: friends, neighbors, etc.	5	22.8
Bank loans	1	4.5

Of twenty-two patients with anti-HER2 therapy, the family contribution was the dominant solution of payment with 68.2%, while only one patient could personally afford the whole cost of anti-HER2 therapy. Other options were from patients' social relationships (22.8%) or bank loans (4.5%).

E t	Anti-HER				
Factors		Yes (n, %)	No (n, %)	p-value	
Age	< 60 years old	17 (77.3%)	38 (66.7%)	0.358	
	\geq 60 years old	5 (22.7%)	19 (33.3%)		
Stage	I, II, III	21 (95.5%)	52 (91.2%)	0.525	
	IV	1 (4.5%)	5 (8.8%)	0.323	
Knowledge about HER2- targeted therapy	Sufficient	20 (90.9%)	34 (59.6%)	0.007	
	Normal	2 (9.1%)	23 (40.4%)	0.007	

 Table 5: Treatment-decision-making factors

The highlighting features of BC patients assigned to anti-HER2 therapy were < 60 years old (77.3%), non-metastasic stage (95.5%), and having sufficient knowledge about the therapy (90.9%). A significant correlation between treatment decision-making and knowledge of HER2-targeted therapy was revealed (p = 0.007).

IV. DISCUSSION

The mean age of patients participating in this study was 54.14 ± 11.03 , in which the age group of 50-59 accounted for the majority at 39.2%. The most common clinical symptom was newonset breast pain, presented in 15 patients (19%), and others were found only in a few patients, including nipple discharge, changes in breast skin, orange peel texture, etc. In only 25.4% of cases, mammography was indicated. Of 26 patients taking mammography, the BIRADS 5 was the most common with 60.7%. The highest percentage of histological subtypes was invasive ductal carcinoma with 60%, while the portion of invasive lobular carcinoma was only 3.8%. A study by Fan et al (2021) showed a similar result, in which the most common subtype was also invasive ductal carcinoma (87.1%) [14]. According to Arpino et al (2015), this kind of subtype accounted for 91.0% [15]. All patients in our study showed HER2 (3+) on ICH, therefore, there was not any case that required the confirmation by FISH test.

Of 79 patients with HER2 positive in our study, only 22 patients underwent anti-HER2 therapy (27.8%) with trastuzumab (21 cases) or trastuzumab plus pertuzumab (1 case). Trapani et at (2021), investigating different cancer centers in 45 countries, concluded that trastuzumab was

unavailable in 8% of the centers in their studies, of which 60% were in low-middle-income countries [11]. Research conducted in Africa by Vanderpuye et al (2016) indicated that 53% of cancer centers in Africa had Trastuzumab in their available drug catalog, and only 5% of patients could afford the cost of this therapy [16]. Even though 100% of patients had health insurance which covered 60% of Trastuzumab treatment cost, the percentage of patients assigned to this therapy was low. However, the most common reason for this finding was due to financial difficulties or lack of treatment affordability, which accounted for 96.5% of patients refusing anti-HER2 therapy. Our study also revealed that the cost of treatment with trastuzumab per person for each cycle ranged from 10.5 million to 13.0 million Vietnam Dong (approximately 445 - 550 USD). This was an obvious financial burden for patients and their families to pay for the total 18 cycles of trastuzumab according to Vietnamese Ministry of Health guidelines and National Comprehensive Cancer Network (NCCN) guidelines for breast cancer [17,18]. According to a survey by the General Statistics Office of Vietnam, the average income per capita in Vietnam was approximately 56 million Vietnam Dong per year [19]. Therefore, most patients in Vietnam could hardly afford the cost of trastuzumab-

based treatment. In 2017, the European Society for Medical Oncology (ESMO) reported that the difficulty in approaching trastuzumab-based treatment included the lack of reliable pharmacy suppliers and a limited budget for treatment [20]. Among patients undergoing trastuzumab treatment in this study, only 4.5% of patients can afford the treatment fee by themselves. The others required financial support from their relatives (68.2%), other sources (22.7%), or even bank loans (4.5%). Hence, our findings once again emphasize the cost of anti-HER2 therapy was a socio-economical burden.

The anti-HER2 comprehension of patients and relatives significantly correlates to the decision-making of this treatment (p = 0.007). By consulting in detail and providing the evidencebased benefit of trastuzumab on patients with positive HER2, clinicians play a decisive role in patients' attitudes toward cost-efficiency consideration. Of all 22 patients with trastuzumab treatment, 17 patients were in the age group of under 60 (77.3%). This group was demonstrated to have the best cost-efficiency benefit by Chan et al (2009) [12]. Although age was a decisionmaking factor investigated in our study, there was no significant difference in the choice of treatment between patients under and over 60 years old (p = 0.358). On the staging-related perspective, patients with non-metastasic disease tend to dominantly participate in anti-HER2 treatment (95.5%), while the proportion of stage-IV breast cancer assigned to trastuzumab was only 4.5%. We suggested that metastatic disease may contribute to the refusal of treatment. Nevertheless, more studies should be established in this field.

V. CONCLUSION

Among patients diagnosed with positive HER2 breast cancer, invasive ductal carcinoma was the most common subtype and stage II was the dominant in this study. About one-third of patients underwent anti-HER2 therapy with the trastuzumabbased regimen. The financial difficulties and lack of treatment affordability were the main barriers to this highly effective therapy. The correlation between anti-HER2 therapy knowledge and decision-making emphasized the role of clinicians in patients' consideration of treatment.

REFERENCE

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.
- 2 Slamon D, Eiermann W, Robert N, Pienkowski T, et al; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-83.
- 3 Shah S, Chen B. Testing for HER2 in Breast Cancer: A Continuing Evolution. Patholog Res Int. 2010;2011:903202.
- 4 Baselga J, Swain SM. CLEOPATRA: a phase III evaluation of pertuzumab and trastuzumab for HER2positive metastatic breast cancer. Clin Breast Cancer. 2010;10(6):489-91.
- 5 Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, et al; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659-72.
- 6 Romond EH, Perez EA, Bryant J, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673-84.
- 7 Early Breast Cancer Trialists' Collaborative group (EBCTCG). Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials. Lancet Oncol. 2021;22(8):1139-1150.
- 8 Ellegård S, Engvall K, Asowed M, Hallbeck AL, Elander N, Stål O. Long-term follow-up of early stage HER2positive breast cancer patients treated with trastuzumab: A population-based real world multicenter cohort study. Front Oncol. 2022;12:861324.
- 9 Wynn CS, Tang SC. Anti-HER2 therapy in metastatic breast cancer: many choices and future directions. Cancer Metastasis Rev. 2022;41(1):193-209.
- 10 Swain SM, Baselga J, Kim SB, Ro J, et al; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724-34.
- 11 Trapani D, Lengyel CG, Habeeb BS, Altuna SC, et al. The global landscape of availability, accessibility and affordability of essential diagnostics and therapeutics for the management of HER2-positive breast cancer: The ONCOLLEGE-001 survey. J Cancer Policy. 2021;28:100285.

- 12 Chan AL, Leung HW, Lu CL, Lin SJ. Cost-effectiveness of trastuzumab as adjuvant therapy for early breast cancer: a systematic review. Ann Pharmacother. 2009;43(2):296-303.
- 13 Wolff AC, Hammond ME, Hicks DG, Dowsett M, et al; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31(31):3997-4013.
- 14 Fan Y, Wang Y, He L, Imani S, Wen Q. Clinical features of patients with HER2-positive breast cancer and development of a nomogram for predicting survival. ESMO Open. 2021;6(4):100232.
- 15 Arpino G, Michelotti A, Truini M, Montemurro F, et al. Demographic, tumor and clinical features of clinical trials versus clinical practice patients with HER2-positive early

breast cancer: results of a prospective study. J Cancer Res Clin Oncol. 2016;142(3):669-78.

- 16 Vanderpuye VDNK, Olopade OI, Huo D. Pilot Survey of Breast Cancer Management in Sub-Saharan Africa. J Glob Oncol. 2016;3(3):194-200.
- 17 Gradishar WJ, Moran MS, Abraham J, Aft R, et al. Breast Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(6):691-722.
- 18 Bộ Y Tế. Hướng dẫn chẳn đoán và điều trị ung thư vú. 2020; 44-46.
- 19 Tổng Cục Thống Kê. Thông báo cáo chí về kết quả khảo sát mức sống dân cư năm 2022. Bộ Kế Hoạch và Đầu Tư. 2022.
- 20 Cherny NI, Sullivan R, Torode J, Saar M, Eniu A. ESMO International Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in countries outside of Europe. Ann Oncol. 2017;28(11):2633-2647.