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REVIEW ARTICLE

HER2-positive Metastatic Breast Cancer: New Agents on the Horizon

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ABSTRACT

The human epidermal growth factor receptor HER2/neu gene is amplified and overexpressed in 25 to 30% of breast cancers. In women with HER2-positive advanced or metastatic breast cancer, the anti-HER2 monoclonal antibody trastuzumab and the dual tyrosine kinase inhibitor lapatinib are both established options used in combination with cytotoxic chemotherapy. In patients who progress after first-line therapy with trastuzumab plus chemotherapy, continued trastuzumab or switching to lapatinib, both in combination with cytotoxic chemotherapy, offers clinical benefit. New agents in the metastatic disease setting include pertuzumab and trastuzumab emtansine. In the first-line setting, the addition of pertuzumab to trastuzumab/docetaxel yields longer median progression-free survival than placebo plus trastuzumab/docetaxel (18.5 vs. 12.4 months; p < 0.001). In the second-line setting, trastuzumab emtansine alone improves median progression-free survival compared with capecitabine plus lapatinib (9.6 vs. 6.4 months; p < 0.0001). The combination of trastuzumab emtansine plus pertuzumab has also shown encouraging preliminary activity. Other agents in clinical development include subcutaneous trastuzumab, afatinib, and neratinib. Numerous other treatments across a range of drug classes are currently in development for the treatment of HER2-positive metastatic breast cancer.

Key Words: *Antineoplastic agents; Breast neoplasms; Hormone replacement therapy*

中文摘要

HER-2陽性轉移性乳癌：現有的新製劑

楊明明

25%至30%的乳癌有人類表皮生長因子受體2（HER2）／neu基因放大和過度表現的情況。晚期或轉移性HER-2陽性乳癌的患者中，抗HER2單株抗體trastruzumab以及雙酪胺酸激酶抑制劑lapatinib，都是可以結合細胞毒性化療的已知選擇。對於接受trastruzumab和化療的第一線治療後仍有惡化的患者，繼續trastruzumab治療或者改為lapatinib治療，而再結合化療，可以有臨床上的好處。治療轉移性乳癌的新製劑包括有pertuzumab和trastuzumab emtansine。第一線治療中，與沒有加入pertuzumab的治療比較，在trastuzumab/docetaxel加入pertuzumab會有較長的無惡化存活期中位數（前者為12.4個月，後者為18.5個月；p < 0.001）。第二線治療中，與capecitabine結合lapatinib的治療比較，trastuzumab emtansine可改善無惡化存活期中位數（前者為6.4個月，後者為9.6個月；p < 0.0001）。結合trastuzumab emtansine及pertuzumab的治療在初步試驗中出現鼓舞性的結果。其他製劑包括作皮下注射的trastuzumab、afatinib和neratinib正處於臨床研究階段。目前正開發許多針對HER-2陽性轉移性乳癌的一系列藥物治療。

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INTRODUCTION

The human epidermal growth factor receptor (EGFR) *HER2* gene, which encodes the growth factor receptor HER2, is amplified and overexpressed in 25 to 30% of breast cancers. HER2-positive tumours have been associated with more aggressive disease. In recent years, HER2 has become an important biomarker and target of therapy for breast cancer. In particular, inhibiting the signalling activity of HER2 with HER2-targeted therapies has advanced the treatment of locally advanced or metastatic breast cancer (MBC). In this setting, the incorporation of trastuzumab and lapatinib has become an integral part of the therapeutic armamentarium. This review considers these established therapies together with other emerging targeted therapies in locally advanced or MBC.

APPROVED ANTI-HER2 AGENTS

In women with HER2/neu-overexpressing advanced or MBC, the anti-HER2 monoclonal antibody trastuzumab is used in the first-line setting in combination with cytotoxic chemotherapy.[1] In a landmark study reported by Slamon et al[1] over a decade ago, this combination was shown to significantly prolong overall survival (OS) compared with chemotherapy alone. In this study, the median OSs were 25.1 and 20.3 months in the trastuzumab-containing arm and the chemotherapy-alone arm, respectively (p = 0.01). Although standard chemotherapy consisted of paclitaxel or doxorubicin / cyclophosphamide, trastuzumab has subsequently been combined with other agents including docetaxel[2] and vinorelbine,[3] and such combinations have shown high response rates when compared with either cytotoxic agent alone. For instance, docetaxel in combination with trastuzumab achieved an overall response rate (ORR) of 61% and a median OS of 31.2 months compared with 34% and 22.7 months, respectively, for docetaxel alone.[2]

Lapatinib, a dual tyrosine kinase inhibitor (TKI) that interrupts both HER2/neu and EGFR pathways, is another approved agent for the treatment of advanced or MBC. A phase III study recently compared taxane-based therapy with either lapatinib or trastuzumab as first-line treatment of HER2-positive MBC.[4] While the combination of lapatinib plus taxane was associated with a significantly shorter progression-free survival (PFS; median PFS, 8.8 vs. 11.4 months; hazard ratio [HR] = 1.33; 95% confidence interval [CI], 1.06-1.67; p = 0.01), no difference in survival was detected.

BEYOND FIRST-LINE TRASTUZUMAB / CHEMOTHERAPY

In patients who progress after first-line therapy with trastuzumab plus chemotherapy, the combination of lapatinib and capecitabine has been shown to improve time to progression (TTP) compared to capecitabine alone (median TTP, 8.4 vs. 4.4 months), although this did not translate into a significant benefit in OS.[5] The continuation of trastuzumab beyond first-line therapy has been evaluated in another study.[6] In this latter study, patients with HER2-positive breast cancer that progressed during trastuzumab treatment were randomised to capecitabine with or without continuation of trastuzumab. The main efficacy findings are shown in Table 1.[6,7] Briefly, the primary endpoint of TTP, as well as other study endpoints including ORR and clinical benefit rate (CBR), were significantly improved in patients who continued with trastuzumab. However, the OS was not demonstrated to be superior in the trastuzumab-continuing arm; this could have been related to the lack of statistical power due to a small patient sample accrued. Although 482 patients were planned for enrolment, accrual was stopped prematurely due to the availability of lapatinib as second-line treatment in Europe during the course of the trial.

For patients with HER2-positive trastuzumab-refractory MBC, the combination of lapatinib and trastuzumab has been evaluated in a phase III study that compared lapatinib alone or in combination with trastuzumab.[8] In the lapatinib only arm, crossover to combination therapy

Table 1. Efficacy outcomes in patients with HER2-positive metastatic breast cancer who progressed during first-line trastuzumab therapy: continuation of trastuzumab in combination with capecitabine compared with capecitabine alone.[6,7]

Efficacy outcome	Capecitabine (n = 78)	Trastuzumab plus capecitabine (n = 78)	OR or HR for outcome	p Value
Overall response rate (%)	27.0	48.1	OR = 2.50	0.0115
Clinical benefit rate (%)	54.1	75.3	OR = 2.59	0.0068
Time to progression (months)	5.6	8.2	HR = 0.69	0.0338
Overall survival* (months)	20.6	24.9	HR = 0.94	0.73

Abbreviations: HR = hazard ratio; OR = odds ratio.

* After 20.7 months of follow-up.

was permitted if a patient experienced progression after at least four weeks of single-agent therapy. Patients in this study had received a median of three prior trastuzumab-containing regimens, indicating a heavily pre-treated population. The combination of lapatinib and trastuzumab was superior to lapatinib alone in terms of PFS (median PFS, 12.0 vs. 8.1 weeks; HR = 0.73; 95% CI, 0.57-0.93; p = 0.008) and CBR (24.7% vs 12.4%; p = 0.01). A trend for improved OS was also observed in the combination arm (HR = 0.75; 95% CI, 0.53-1.07; p = 0.106). ORR was similar for the combination and lapatinib-only arms (10.3% vs. 6.9%, respectively; p = 0.46). Diarrhoea, rash, nausea, and fatigue were the most common adverse events, with diarrhoea being significantly more frequent in the combination arm (p = 0.03).

NEW AGENTS FOR HER2-POSITIVE METASTATIC BREAST CANCER

Inhibition of the signalling activity of individual receptors in the EGFR family has advanced the treatment of a range of cancers, with HER2 and HER3 being particularly important in breast cancer.[9] Novel therapies with mechanisms of action that target cell signalling pathways via inhibition of these receptors include TKIs, antibody-chemotherapy conjugates, heat shock protein inhibitors, and antibodies that interfere with the formation of HER2/HER3 dimers.

One new agent with promising activity in the treatment of first-line HER2-positive MBC is pertuzumab, an anti-HER2 humanised monoclonal antibody that inhibits HER2-HER3 receptor dimerisation and has a complementary mechanism of action to trastuzumab.[10] In the phase III CLinical Evaluation Of Pertuzumab And TRAstuzumab (CLEOPATRA) study, 808 patients with HER2-positive MBC were randomised to receive either pertuzumab in combination with trastuzumab and docetaxel or placebo plus trastuzumab/docetaxel as first-line treatment until disease progression.[10] Approximately 11% of patients in each treatment arm had received prior trastuzumab as a component of adjuvant or neoadjuvant therapy. The primary endpoint of independently assessed PFS was significantly longer in the pertuzumab arm when compared with the placebo arm (median PFS, 18.5 vs. 12.4 months; HR = 0.62; 95% CI, 0.51-0.75; p < 0.001). Among patients with no prior adjuvant or neoadjuvant trastuzumab treatment, a significantly better median PFS of 21.6 months was observed in the pertuzumab arm compared with 12.6 months in the placebo arm (HR = 0.60; 95% CI, 0.43-0.83). However, among patients who had received prior adjuvant or neoadjuvant trastuzumab, there was no difference in PFS between the two groups; PFS was 16.9 months in the pertuzumab arm and 10.4 months in the placebo arm (HR = 0.62; 95% CI, 0.35-1.07). In the exploratory analysis, 80.2% of patients in the pertuzumab arm had an objective response, including 5.5% with a complete response (CR) and 74.6% with a partial response (PR) [p = 0.0011]. In comparison, 69.3% of patients in the placebo arm had an objective response, including 4.2% with a CR and 65.2% with a PR. After a median follow-up of 19.3 months, a predefined interim analysis of OS showed a strong trend in favour of pertuzumab compared with placebo (HR = 0.64; 95% CI, 0.47-0.88; p = 0.0053) [Figure]. However, the difference between treatment arms for the interim OS analysis did not cross the pre-specified O'Brien-Fleming stopping boundary (HR ≤ 0.603; p ≤ 0.0012). Independently adjudicated left ventricular systolic dysfunction occurred in 1% of patients in each arm, whereas fall in left ventricular ejection fraction to <50% and by >10% points from baseline occurred in 3.8% of patients in the pertuzumab arm compared with 6.6% of patients in the placebo arm; no increase in cardiac toxicity was found in the experimental arm. Diarrhoea, rash, mucosal inflammation, dry skin, and febrile neutropenia were more common in the pertuzumab arm, whereas peripheral oedema and constipation were more common in the placebo arm. The most common grade 3 or higher adverse events were neutropenia (pertuzumab 48.9% vs. placebo 45.8%), febrile neutropenia (13.8% vs. 7.6%), leukopenia (12.3% vs. 14.6%), and diarrhoea (7.9% vs. 5.0%).[10]

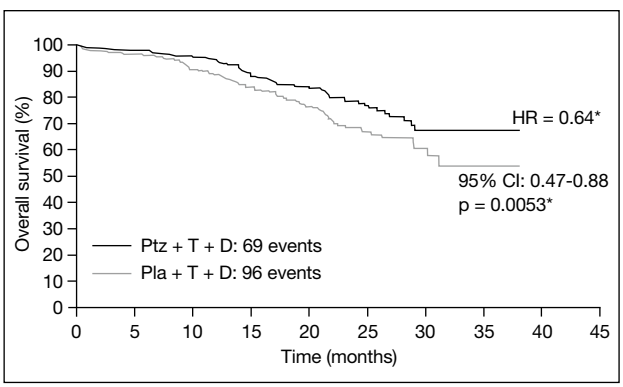

Figure. Overall survival in patients with HER2-positive metastatic breast cancer who received first-line therapy with trastuzumab and docetaxel plus either pertuzumab or placebo.
Abbreviations: HR = hazard ratio; CI = confidence interval.
* The interim OS analysis did not cross the pre-specified O'Brien-Fleming stopping boundary (HR ≤ 0.603; p ≤ 0.0012).

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate comprising trastuzumab (T) and the potent cytotoxic agent mertansine (DM1). T-DM1 has been evaluated for use in the second-line MBC setting in a recent phase III study (the EMILIA study).[11] Patients (n = 978) with HER2-positive locally advanced or MBC previously treated with trastuzumab and a taxane were randomised to receive T-DM1 or capecitabine plus lapatinib until progression or unacceptable toxicity. As many as 88% of patients had received prior therapy for MBC; although all patients had received prior trastuzumab therapy, trastuzumab was administered for early breast cancer in only 16% of the patients. Median dose intensity was 99.9% in the T-DM1 arm compared with 77.2% for capecitabine and 93.4% for lapatinib. The primary endpoint of independently assessed PFS significantly favoured T-DM1 compared with capecitabine/lapatinib (median PFS, 9.6 vs. 6.4 months; HR = 0.650; 95% CI, 0.55-0.77; $p < 0.0001$). An interim analysis of OS showed a strong trend towards longer OS in the T-DM1 arm (median OS not reached vs. 23.3 months; HR = 0.621; 95% CI, 0.48-0.81; $p = 0.0005$). However, the difference between treatment arms for the interim OS analysis did not cross the pre-specified O'Brien-Fleming trial-stopping boundary (HR = 0.617; $p = 0.0003$). ORR significantly favoured T-DM1 compared with capecitabine/lapatinib (ORR = 43.6% vs. 30.8%; $p = 0.0002$), and duration of response (DOR) was almost twice as long with T-DM1 (DOR, 12.6 vs. 6.5 months). Grade 3 or higher adverse events occurred in 40.8% of patients treated with T-DM1 compared with 57.0% of patients treated with capecitabine/lapatinib; adverse events leading to treatment discontinuation occurred in 5.9% versus 10.7%, respectively; adverse events leading to death on treatment occurred in 0.2% versus 1.0%, respectively. A summary of the important non-haematological adverse events is shown in Table 2. Grade 3 or 4 thrombocytopenia occurred in 12.8% of patients treated with T-DM1 but grade 3 or 4 haematological adverse events were otherwise infrequent.

Table 2. Non-haematological adverse events* with incidence ≥2% in patients with HER2-positive metastatic breast cancer who received second-line treatment with either trastuzumab emtansine or capecitabine plus lapatinib.[11]

Adverse event	Capecitabine + lapatinib (n = 488)		Trastuzumab emtansine (n = 490)	
	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)
Diarrhoea	79.7	20.7	23.3	1.6
Hand-foot syndrome	58.0	16.4	1.2	0.0
Vomiting	29.3	4.5	19.0	0.8
Hypokalaemia	8.6	4.1	8.6	2.2
Fatigue	27.9	3.5	35.1	2.4
Nausea	44.7	2.5	39.2	0.8
Mucosal inflammation	19.1	2.3	6.7	0.2
Increased AST	9.4	0.8	22.4	4.3
Increased ALT	8.8	1.4	16.9	2.9

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.
* After 20.7 months of follow-up.

ONGOING TRIALS IN HER2-POSITIVE METASTATIC BREAST CANCER

T-DM1 has also been evaluated in the first-line MBC setting in a randomised phase II trial comparing this agent with trastuzumab plus docetaxel.[12] Again, the primary endpoint of PFS significantly favoured treatment with T-DM1 compared with trastuzumab/docetaxel (median PFS, 14.2 vs. 9.2 months; HR = 0.594; 95% CI, 0.364-0.968; $p = 0.0353$). In a phase Ib/II single-arm study, the combination of T-DM1 plus pertuzumab showed encouraging preliminary activity both in the first-line setting and in patients with relapsed MBC.[13] In first-line MBC, a phase III study is currently evaluating T-DM1 with either pertuzumab or placebo, with a third arm consisting of trastuzumab plus taxane as the control.[14] The trial has adopted a superiority design with planned non-inferiority analyses, with PFS being the primary study endpoint. At the same time, an alternative formulation of trastuzumab is also being evaluated. Preliminary data suggest that subcutaneous trastuzumab has comparable drug exposure, safety, and efficacy when compared with the intravenous formulation, with subcutaneous administration offering greater convenience. Therefore, a phase III study is currently evaluating subcutaneous versus intravenous trastuzumab in the adjuvant and neoadjuvant setting.[15]

Afatinib is a TKI that irreversibly inhibits signalling through activated EGFR (ErbB1), HER2 (ErbB2) and ErbB4 receptors, and transphosphorylation of HER 3 (ErbB3). As a candidate drug for breast cancer, afatinib is currently being evaluated in a range of settings. In a phase II neoadjuvant study of patients with HER2-positive stage IIIa-c breast cancer, single-agent afatinib showed a high objective response rate, with 70% of patients achieving a PR compared with 75.0% for lapatinib and 36.4% for trastuzumab.[16] In the HER2-positive first- and second-line MBC setting, a phase III study is currently evaluating treatment with afatinib or

trastuzumab, both in combination with vinorelbine.[17] Afatinib is also being evaluated in phase II studies as monotherapy in HER2-positive MBC patients who progress following neoadjuvant or adjuvant therapy,[18] and as monotherapy in HER2-positive breast cancer with progressive brain metastases after trastuzumab- or lapatinib-based therapy.[19]

Two other agents in late-stage clinical development are worth mentioning. Neratinib, another irreversible pan-ErbB receptor TKI, has shown good activity in patients with and without prior trastuzumab treatment.[20] Everolimus, an oral inhibitor of mammalian target of rapamycin, is currently being evaluated in a phase III trial in combination with trastuzumab and paclitaxel as first-line therapy in HER2-positive MBC.[21]

CONCLUSIONS

In women with HER2-positive MBC, data are available for HER2-targeted therapy in the first-line setting with trastuzumab or lapatinib in combination with cytotoxic chemotherapy. However, the combination of trastuzumab, pertuzumab, and a taxane has also been approved in the United States for use in this setting, and may offer additional benefits beyond two-agent therapy. When looking beyond first-line therapy, available data support the use of lapatinib plus capecitabine, trastuzumab plus capecitabine, and trastuzumab plus lapatinib. In addition, T-DM1 is emerging as a potential candidate in the second-line setting, having demonstrated superior PFS compared with lapatinib plus capecitabine. Numerous other treatments across a range of drug classes are currently in development for the treatment of HER2-positive breast cancer.

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