case1

Herceptin継続

2010.03.07
中部乳癌会議
Aグループ

Case 1

- 現在63歳、59歳時に左乳癌（広範なDCISを伴う浸潤癌）で乳房切除術施行（Bt+SLNB）。
- 病理結果：invasive ductal carcinoma, IIa1, t=15x8mm, HG:3, n:0/1(SLN), ER:0, PgR:0, HER2:3+, Ly(-), v(-).
- 術後AC x 4cycle施行（Hereceptin保険適応なし）
- 術後2年で、肝転移（4cm)出現。
- Herceptin + weekly paclitaxelk開始して3カ月でCRとなる。6カ月まで同治療継続した後に、Herceptin単剤に変更して、2年間CRが継続中である（PET異常なし、腫瘍マーカー正常）。
- Herceptinを継続するかどうか本人も迷っている（金銭的な面もあり）

Herceptin継続 vs Herceptin中止

論点整理

・再発乳がんであること
・画像上とらえられない微小転移が残存しており「治癒」の状態ではないと考える

ポイント

・Herceptinを継続する医学的risk and benefit
・患者の社会的、心理的な迷い（=不安）

• CR後の長期投与に関するエビデンスはない

↓

PD後のHerceptin継続の有無を見た報告

Journal of Clinical Oncology, Vol 27, No 12 (April 20), 2009: pp. 1999-2006

Trastuzumab Beyond Progression in Human Epidermal Growth Factor Receptor 2–Positive Advanced Breast Cancer: A German Breast Group 26/Breast International Group 03-05 Study

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Purpose Trastuzumab shows clinical activity in human epidermal growth factor receptor 2 (HER-2)–positive early and advanced breast cancer. In the German Breast Group 26/Breast International Group 03-05 trial, we investigated if trastuzumab treatment should be continued beyond progression.

Methods Patients with HER-2–positive breast cancer that progresses during treatment with trastuzumab were randomly assigned to receive capecitabine (2,500 mg/m^2 body-surface area on days 1 through 14 [1,250 mg/m^2 semi-daily]) alone or with continuation of trastuzumab (6 mg/kg body weight) in 3-week cycles. The primary end point was time to progression.

Results We randomly assigned 78 patients to capecitabine and 78 patients to capecitabine plus trastuzumab. Sixty-five events and 38 deaths in the capecitabine group and 62 events and 33 deaths in the capecitabine-plus-trastuzumab group occurred during 15.6 months of follow-up. Median times to progression were 5.6 months in the capecitabine group and 8.2 months in the capecitabine-plus-trastuzumab group with an unadjusted hazard ratio of 0.69 (95% CI, 0.48 to 0.97; two-sided log-rank P = .0338). Overall survival rates were 20.4 months (95% CI, 17.8 to 24.7) in the capecitabine group and 25.5 months (95% CI, 19.0 to 30.7) in the capecitabine-plus-trastuzumab group (P = .257). Overall response rates were 27.0% with capecitabine and 48.1% with capecitabine plus trastuzumab (odds ratio, 2.50; P = .0115). Continuation of trastuzumab beyond progression was not associated with increased toxicity.

Conclusion Continuation of trastuzumab plus capecitabine showed a significant improvement in overall response and time to progression compared with capecitabine alone in women with HER-2–positive breast cancer who experienced progression during trastuzumab treatment.

Supported by Roche AG, Germany, and by the University College London Hospitals/University College London (UCLH/UCL) Comprehensive Biomedical Research Centre (R.C.S.).

Journal of Clinical Oncology, Vol 28, No 7 (March 1), 2010: pp. 1124-1130

Randomized Study of Lapatinib Alone or in Combination With Trastuzumab in Women With ErbB2-Positive, Trastuzumab-Refractory Metastatic Breast Cancer

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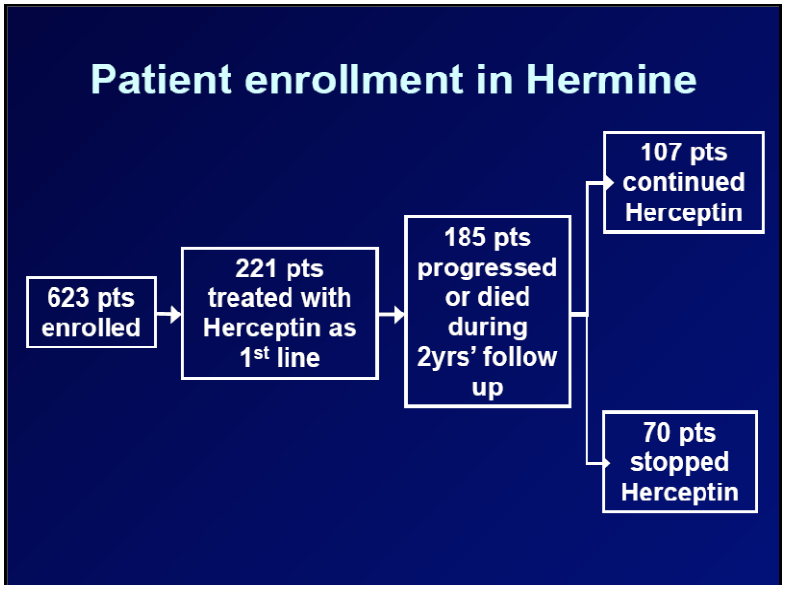
Purpose Preclinical studies in ErbB2-positive cell lines demonstrated a synergistic interaction between lapatinib and trastuzumab, suggesting that dual blockade is more effective than a single agent alone. EGF104900 compared the activity of lapatinib alone or in combination with trastuzumab in patients with ErbB2-positive, trastuzumab-refractory metastatic breast cancer (MBC).

Patients and Methods Patients with ErbB2-positive MBC who experienced progression on prior trastuzumab-containing regimens were randomly assigned to receive either lapatinib alone or in combination with trastuzumab. The primary end point was progression-free survival (PFS). Secondary efficacy end points included overall response rate (ORR), clinical benefit rate (CBR; complete response, partial response, and stable disease for ≥ 24 weeks), and overall survival (OS).

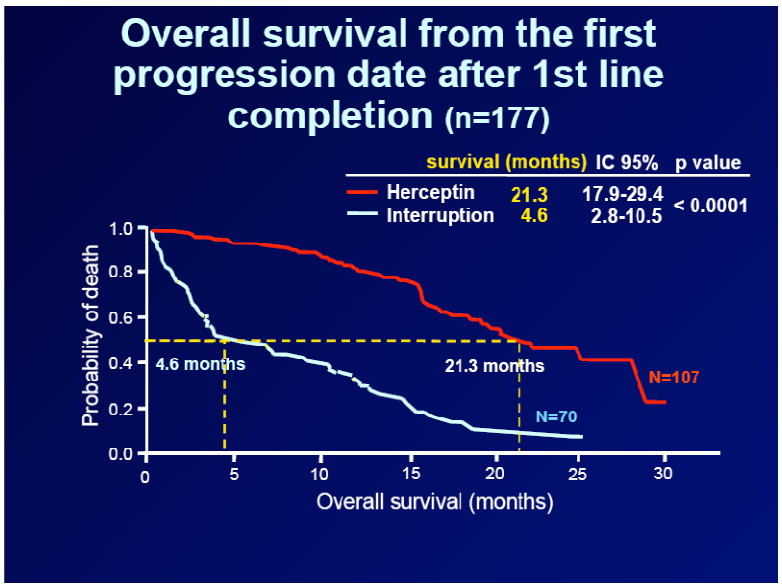
Results In the intent-to-treat population (N = 296) who received a median of three prior trastuzumab-containing regimens, the combination of lapatinib with trastuzumab was superior to lapatinib alone for PFS (hazard ratio [HR] = 0.73; 95% CI, 0.57 to 0.93; P = .008) and CBR (24.7% in the combination arm *v* 12.4% in the monotherapy arm; P = .01). A trend for improved OS in the combination arm was observed (HR = 0.75; 95% CI, 0.53 to 1.07; P = .106). There was no difference in ORR (10.3% in the combination arm *v* 6.9% in the monotherapy arm; P = .46). The most frequent adverse events were diarrhea, rash, nausea, and fatigue; diarrhea was higher in the combination arm (P = .03). The incidence of symptomatic and asymptomatic cardiac events was low (combination therapy = 2% and 3.4%; monotherapy = 0.7% and 1.4%, respectively).

Conclusion Despite disease progression on prior trastuzumab-based therapy, lapatinib in combination with trastuzumab significantly improved PFS and CBR versus lapatinib alone, thus offering a chemotherapy-free option with an acceptable safety profile to patients with ErbB2-positive MBC.



Results

	Continued Herceptin	Stopped Herceptin
Duration of treatment (months)	**24.7** (21.7-24.9)	**6.1** (5.6-8.5)
Median TTP (months)	**10.2** (9.1-11.5)	**7.1** (6.1-7.9)



Herceptinの長期投与における安全性

Long-Term Cardiac Tolerability of Trastuzumab in Metastatic Breast Cancer: The M.D. Anderson Cancer Center Experience

Valentina Guarneri, Daniel J. Lenihan, Vicente Valero, Jean-Bernard Durand, Kristine Broglio, Kenneth R. Hess, Laura Boehnke Michaud, Ana M. Gonzalez-Angulo, Gabriel N. Hortobagyi, and Francisco J. Esteva

A B S T R A C T

Purpose
To evaluate the cardiac safety of long-term trastuzumab therapy in patients with human epidermal growth receptor 2 (HER2) –overexpressing metastatic breast cancer (MBC) treated at The University of Texas M.D. Anderson Cancer Center (Houston, TX).

Patients and Methods
Among 218 MBC patients treated with trastuzumab-based therapy for at least 1 year, 173 patients were assessable for cardiac toxicity. Cardiac events (CEs) were defined as follows: asymptomatic decrease of left ventricular ejection fraction (LVEF) below 50%; decrease of 20 percentage points in LVEF compared with the baseline; or signs or symptoms of congestive heart failure (CHF).

Results
The median cumulative time for trastuzumab administration was 21.3 months. The median follow-up was 32.6 months (range, 11.8 to 79.0 months). Forty-nine patients (28%) experienced a CE: three patients (1.7%) had an asymptomatic decrease in the LVEF of 20 percentage points, 27 patients (15.6%) experienced grade 2 cardiac toxicity, and 19 patients (10.9%) experienced grade 3 cardiac toxicity. All but three patients had improved LVEF or symptoms of CHF with trastuzumab discontinuation and appropriate therapy. There was one cardiac-related death (0.5%). Baseline LVEF was significantly associated with CE (hazard ratio, 0.94; $P = .001$). The hazard of a CE among patients taking concomitant taxanes was higher early in the follow-up period but declined during the course of follow-up.

Conclusion
The risk of cardiac toxicity of long-term trastuzumab-based therapy is acceptable in this population, and this toxicity is reversible in the majority of the patients. In patients who have experienced a CE, additional treatment with trastuzumab can be considered after recovery of cardiac function.

J Clin Oncol 24:4107-4115. © 2006 by American Society of Clinical Oncology

論点整理

・再発乳がんであること

・画像上とらえられない微小転移が残存しており「治癒」の状態ではないと考える

ポイント

・Herceptinを継続する医学的risk and benefit

・患者の社会的、心理的な迷い（=不安）

高額療養費

同じ人が同じ月内に、同一の医療機関に支払った自己負担額が、限度額（下表自己負担限度額）を超えるときは、超えた額を高額療養費として支給されます。但し、差額ベッド料や保険のきかない治療による超過分、食事代等は対象になりません。

自己負担限度額

被保険者が、同一月に、医療機関ごとに、入院・通院・医科・歯科別で支払う自己負担額が下表の金額を超えるとき、その超えた分について高額療養費の支給が受けられます。
(注)税制法改正により、自己負担限度額が下表と異なる場合があります。

平成１８年１０月１日から			
70歳未満の方	上位所得世帯※	１５０，０００円＋（実際にかかった医療費－５００，０００円）×１%	
	一般	８０，１００円＋（実際にかかった医療費－２６７，０００円）×１%	
	住民税非課税世帯	３５，４００円	
		外来	外来＋入院
70歳以上の方	一定以上所得者※※	４４，４００円	８０，１００円＋（実際にかかった医療費－２６７，０００円）×１%
	一般	１２，０００円	４４，４００円
	住民税非課税世帯	８，０００円	２４，６００円
	住民税非課税世帯であってその世帯の所得が基準額以下の世帯		１５，０００円

４回目以降の自己負担限度額

過去１２ヵ月以内に、同じ世帯で４回以上高額療養費の支給を受けたとき、４回目以降は下表の金額を超えた分が支給されます。

70歳未満の方	上位所得世帯	８３，４００円
	一般	４４，４００円
	住民税非課税世帯	２４，６００円
		外来＋入院
70歳以上の方	一定以上所得者	４４，４００円

月に自己負担２１，０００円以上が２回以上ある場合（７０歳未満の方）

- **2010年春よりハーセプチンの薬価引き下げ**
- 【薬価改定ニュース】
- 市場拡大再算定品目を了承　アクトス、グリベック、ハーセプチンなど
- 2010/01/29
- 厚生労働省は4月に実施する薬価改定での市場拡大再算定品目を提示

- 対象品目は、
- ▽糖尿病治療薬。。。。。。。
- ▽乳がん治療薬「ハーセプチン注射用60」「同150」（中外製薬）ーの5成分8品目。厚労省は改定薬価の案を2月1日の週にも製薬各社に内示、3月上旬に決定・告示する。
-

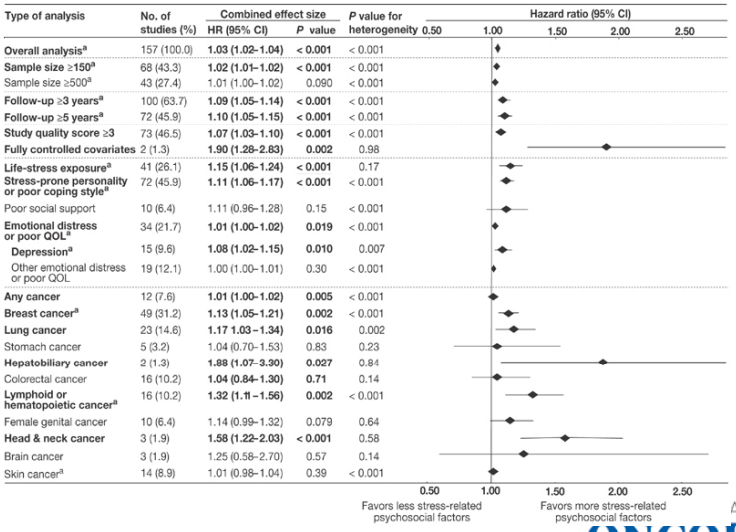
再算定による引き下げ率は市場規模の拡大率をベースに計算されるが、原価計算方式の算定品目は最大25%、類似薬効比較方式の算定品目は最大15%の引下げを受ける。ただ、大規模臨床試験などで「真の臨床的有用性が直接的に検証されていると認められた場合」には、引き下げ率を緩和する補正加算がつく。

がんサバイバーの再発不安

- ストレスとがんの予後との関係を検討した研究報告をメタ解析によって検討した論文によると、ストレスに関連した精神的要因ががんの発生率やがん診断後の生存率に影響することが示唆されています。すなわち、ストレスの多い生活が、がん治療後の生存率を低下させることが報告されています。ストレスを受けやすい性格や、ストレスにうまく対処できない人、物事を悲観的あるいは否定的に捉える傾向の人、生活の質が悪い状態の人では、がんの発生率も再発率も死亡率も高くなっていました。（Nat Clin Pract Oncol., 5(8): 466-475, 2008年）

Figure 3 The effect of stress-related psychosocial factors on cancer survival: results of meta-analyses, subgrouping, and sensitivity analyses

Type of analysis	No. of studies (%)	Combined effect size HR (95% CI)	*P* value	*P* value for heterogeneity
Overall analysis[a]	157 (100.0)	**1.03 (1.02–1.04)**	**< 0.001**	< 0.001
Sample size ≥150[a]	68 (43.3)	**1.02 (1.01–1.02)**	**< 0.001**	< 0.001
Sample size ≥500[a]	43 (27.4)	1.01 (1.00–1.02)	0.090	< 0.001
Follow-up ≥3 years[a]	100 (63.7)	**1.09 (1.05–1.14)**	**< 0.001**	< 0.001
Follow-up ≥5 years[a]	72 (45.9)	**1.10 (1.05–1.15)**	**< 0.001**	< 0.001
Study quality score ≥3	73 (46.5)	**1.07 (1.03–1.10)**	**< 0.001**	< 0.001
Fully controlled covariates	2 (1.3)	**1.90 (1.28–2.83)**	**0.002**	0.98
Life-stress exposure[a]	41 (26.1)	**1.15 (1.06–1.24)**	**< 0.001**	0.17
Stress-prone personality or poor coping style[a]	72 (45.9)	**1.11 (1.06–1.17)**	**< 0.001**	< 0.001
Poor social support	10 (6.4)	1.11 (0.96–1.28)	0.15	< 0.001
Emotional distress or poor QOL[a]	34 (21.7)	**1.01 (1.00–1.02)**	**0.019**	< 0.001
Depression[a]	15 (9.6)	**1.08 (1.02–1.15)**	**0.010**	0.007
Other emotional distress or poor QOL	19 (12.1)	1.00 (1.00–1.01)	0.30	< 0.001
Any cancer	12 (7.6)	**1.01 (1.00–1.02)**	**0.005**	< 0.001
Breast cancer[a]	49 (31.2)	**1.13 (1.05–1.21)**	**0.002**	< 0.001
Lung cancer	23 (14.6)	**1.17 1.03–1.34)**	**0.016**	0.002
Stomach cancer	5 (3.2)	1.04 (0.70–1.53)	0.83	0.23
Hepatobiliary cancer	2 (1.3)	**1.88 (1.07–3.30)**	**0.027**	0.84
Colorectal cancer	16 (10.2)	**1.04 (0.84–1.30)**	**0.71**	0.14
Lymphoid or hematopoietic cancer[a]	16 (10.2)	**1.32 (1.11–1.56)**	**0.002**	< 0.001
Female genital cancer	10 (6.4)	1.14 (0.99–1.32)	0.079	0.64
Head & neck cancer	3 (1.9)	**1.58 (1.22–2.03)**	**< 0.001**	0.58
Brain cancer	3 (1.9)	1.25 (0.58–2.70)	0.57	0.14
Skin cancer[a]	14 (8.9)	1.01 (0.98–1.04)	0.39	< 0.001



AL PRACTICE ONCOLOGY

Chida Y *et al.* (2008) Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nat Clin Pract Oncol* doi:10.1038/ncponc1134

結論

case1

Herceptin継続