symposium article

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Safety and activity of trastuzumab-containing therapies for the treatment of metastatic breast cancer: our long-term clinical experience (GOIM study)

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Background: Trastuzumab is widely used as the treatment of choice for HER2-positive metastatic breast cancer (MBC).

Patients and methods: Seventy patients, median age 57 years and range 31–81 years, were included in our retrospective analysis with the aim to evaluate safety and activity of trastuzumab-containing therapies.

Results: We observed for first-line treatment response rate (RR) 41%, stable disease (SD) 47% and time to progression (TTP) 8 months (range 1–44). Corresponding numbers for second line were RR 23%, SD 62% and (TTP) 9 months (range 3–23) and beyond second line RR 22%, SD 78% and (TTP) 9 months (range 4–19). Overall survival was 19.2 months (3–62 months). The median cumulative dose of trastuzumab administrated was 5286 mg (464–17 940 mg). Trastuzumab was well tolerated. Median left ventricular ejection function (LVEF) at baseline was 62% and at the end of treatment was 59%. The more relevant adverse events consisted of an asymptomatic decrease in LVEF to 40% (baseline 60%) and a grade 3 symptomatic increase in bilirubin.

Conclusion: Trastuzumab-containing therapies in MBC show a good safety and toxicity profile and a remarkable activity even in heavily pretreated women. Patients should benefit from continued trastuzumab therapy, as shown by the maintenance of (TTP) even beyond second-line treatment.

Key words: cardiac safety, clinical experience, heavily pretreated women, metastatic breast cancer, retrospective analysis, trastuzumab

introduction

Breast cancer represents the main cause of cancer morbidity and mortality in women in most countries all over the world [1].

Metastatic breast cancer (MBC) remains an incurable disease, but in the last decade the development of new cytotoxic drugs and combinations and the introduction of novel targeted agents have permitted to lengthen patient's survival and improve quality of life.

The clinical introduction of trastuzumab, a humanized monoclonal antibody directed against the HER2/neu protein, has drastically altered the lives of many women with HER-2-overexpressing tumors. This anticancer agent plays an important role in breast cancer treatment.

Overexpression of HER-2 and amplification of the HER-2 gene occur in 25%–30% of cases of MBC [2] and are usually associated with a particularly aggressive clinical course and consequently with a poor prognosis and shortened overall survival (OS).

Preclinical models have shown a significant antitumor activity of trastuzumab as a single agent [3] and additive or even synergistic effects in combination with chemotherapy drugs commonly used in the treatment of breast cancer, especially taxanes, vinorelbine and platinum agents [4].

On the basis of these encouraging observations, multiple clinical trials were designed in order to investigate safety and clinical activity of trastuzumab in MBC, first as monotherapy and subsequently in combination. The response rates achieved as monotherapy were of 20%–25% as first-line therapy [5] and 10%–15% in patients [6, 7] pretreated with chemotherapy for metastatic disease.

Two pivotal phase III trial compared first-line chemotherapy alone with the combination of chemotherapy with trastuzumab in patients with HER/2-positive MBC [8, 9]. The addition of trastuzumab significantly improved all clinical endpoints [time to progression (TTP), RR, duration of response and survival). In these trials, there was an unexpected high frequency of cardiotoxicity in patients treated with trastuzumab and chemotherapy.

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A retrospective analysis showed that trastuzumab-associated cardiac events mainly occurred with concomitant use of anthracyclines (mainly doxorubicin) [10].

Consequently, this combination is not currently indicated for clinical use. Several trials have investigated the cardiac safety and efficacy of anthracyclines less cardiotoxic than doxorubicin, such as epirubicin or liposomal formulations of doxorubicin combined with trastuzumab [11, 12].

Both pivotal trials demonstrated a favorable safety profile for trastuzumab plus taxanes [8, 9].

This safe and effective combination is recommended as first-line chemotherapy for patients with HER-2-positive MBC.

In order to improve treatment efficacy and for the increasing use of taxanes in the adjuvant setting, new combinations of trastuzumab and chemotherapy drugs, such as vinorelbine, gemcitabine and capecitabine, have been investigated with encouraging results.

One of the most active non-taxane regimen is the combination of trastuzumab with vinorelbine, with RR of 68%–78% as first-line chemotherapy and a good profile of tolerability, also for the absence of alopecia [13].

Some associations of trastuzumab with chemotherapy combinations have shown interesting data of safety and efficacy. The addition of platinum salts to taxanes and trastuzumab has significantly enhanced the efficacy of this combination doublet [14,15,16].

The potential benefit in a responding patient with MBC to continue trastuzumab with a new chemotherapy drug or in monotherapy is a topic of great interest.

Unfortunately, most of the metastatic patients develop disease progression during the treatment.

In these patients, to stop or continue trastuzumab is controversy [17].

In the clinical practice, there is a consensus to continue trastuzumab beyond progression supported by preclinical observations and clinical data, but there are no mature data from randomized trials [18].

Data collected from clinical trials show a good safety profile of trastuzumab combinations and manageable toxic effects that encourage its use in our clinical practice, but an attentive observation is necessary to investigate long-term tolerability, above all in heavily pretreated patients.

We report in this paper our long-term clinical experience on safety and efficacy of trastuzumab as monotherapy or in combination in MBC patients.

patients and methods

We have conducted a retrospective analysis and collected information on 70 women with histological confirmed HER2-positive MBC, who received trastuzumab-based therapy between May 2001 and June 2006. Standard trastuzumab infusion was administrated until disease progression or serious adverse events.

Median age was 57 years and range 31–81 years. Most patients had good performance status at entry (Eastern Cooperative Oncology Group 0 or 1).

Twenty-six patients had positive estrogen and progesterone receptors. Median number of metastatic sites was 2 and range 1–6. Thirty patients had only visceral metastases, 21 in bone or the soft tissue and the remaining 19 patients had metastases in more risk groups.

Most of the women (66%) had received prior chemotherapy in adjuvant or neo-adjuvant setting, with 17 patients receiving anthracycline-based regimens, 2 taxane-containing therapies and 13 both anthracycline- and taxane-based regimens. Adjuvant endocrine therapy was administered in 27 patients.

Ten patients had metastatic disease at the time of primary diagnosis. Twenty-five patients had received a median number of two previous lines of chemotherapy for metastatic disease (range 1–5). Palliative endocrine therapy was administered in 11 patients.

The characteristics of patients are summarized in Table 1.

statistical analysis

Disease responses were recorded according to the Response Evaluation Criteria in Solid Tumors guidelines [19]. Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria system [20] and was recorded for the worst episode occurred.

Table 1. Patients' characteristics

Characteristics	No. of patients (%)
Age (years)	
Median	57
Range	31–81
ECOG performance status	
0	56 (80)
1	12 (17)
2	2 (3)
Estrogen receptors	
Positive	40 (57)
Negative	27 (39)
Unknown	3 (4)
Progesterone receptors	
Positive	28 (40)
Negative	36 (51)
Unknown	6 (9)
Estrogen and progesterone receptors positive	26 (37)
No. of metastatic sites	
1	29 (41)
2	32 (46)
>3	9 (13)
Metastatic sites median (range)	2 (1–6 sites)
Dominant site of disease	
Bone	8 (11)
Visceral	30 (43)
Soft tissue	13 (19)
Bone and visceral	14 (20)
Bone, visceral and soft tissue	5 (7)
Adjuvant or neo-adjuvant chemotherapy	46 (66)
Prior exposure to anthracycline	17
Prior exposure to taxane	2
Prior exposure to both	13
Adjuvant endocrine therapy	27 (39)
Metastatic disease at the diagnosis	10 (14)
Prior therapy for metastatic disease	
Chemotherapy	25 (36)
Endocrine therapy	11 (16)

ECOG, Eastern Cooperative Oncology Group.

Baseline echocardiography data were recorded and the development of left ventricular ejection function (LVEF) during treatment was reported.

(TTP) was defined as the interval from the first day of application of a new therapy line until tumor progression.

OS was calculated from the day of the first administration of trastuzumab-based therapy to the date of death. Patients alive were censored at the date of the last follow-up contact.

We did not perform statistical comparison of the clinical outcomes in different patient settings for the limited number of patients and the descriptive aim of our retrospective analysis particularly focused on long-term tolerability of trastuzumab-based therapy.

results

Trastuzumab was used first time as monotherapy in 12 patients and in combination in 58 patients.

The associations were with vinorelbine ($n = 28$), docetaxel ($n = 17$) and paclitaxel ($n = 13$). Six patients (8%) had a complete response (CR) and 23 (33%) a partial response (PR); 33 (47%) patients showed stable disease (SD) and 8 (12%) had a progressive disease (PD).

Twenty-six patients received a second trastuzumab-containing therapy, 14 as monotherapy and 12 in combination (four patients with vinorelbine, three with taxanes, two with pegylated liposomal doxorubicin and three with gemcitabine).

Responses for second-line treatment were: 6 (23%) patients had PR, 16 (62%) SD and 4 (15%) PD. Further lines of trastuzumab-based regimen were administered in nine patients with an overall response rate of 22%. A patient treated in third line with the association of pegylated liposomal doxorubicin obtained an interesting CR, after a SD in first line and a PR in the second.

Among patients treated in third or fourth line, no PD was recorded and seven patients obtained a good control of the disease. The tumor responses in the different lines are shown in Table 2.

(TTP) was 8 months (range 1–44) in the first-line setting, 9 months (range 3–23) in the second line and also 9 months (range 4–19) beyond second line.

The median OS was 19.2 months with a range of 3–62 months.

Median cumulative dose of trastuzumab administered was 5286 mg (range 464–17 940).

Trastuzumab-based therapy was well tolerated also in combination. Cardiotoxicity was manageable and we did not observed signs or symptoms of congestive heart failure or treatment-related deaths. Median LVEF at baseline was 62% and 59% at the end of trastuzumab (recorded for 43 patients). Only a patient discontinued trastuzumab in combination due to grade 2 asymptomatic decrease in LVEF to 40% (baseline 60%). Six patients experienced a reversible asymptomatic decrease in LVEF between 10% and 15% reversible with a short treatment arrest. Two patients developed reversible tachycardia. A transient increase in transaminases was observed in two patients.

Only a patient discontinued treatment due to grade 3 symptomatic increase in bilirubin.

Fever was recorded in four patients, two after the first infusion. Four patient lamented fatigue and a transient rash developed in a patient. The different observed side-effects related to trastuzumab administration are summarized in Table 3.

Typical toxic effects of the different chemotherapy agents used in the associations were not increased by the concomitant use of trastuzumab.

After a median time of 12 months of trastuzumab therapy (range 4–22), 11 patients (16%) developed brain metastates (BM).

discussion

The clinical introduction of trastuzumab for MBC overexpressing the HER2 protein has changed the clinical outcome of these patients. Trastuzumab can be combined with

Table 2. Tumor response

	No. of patients (%)
First-line response (70 pts)	
ORR	29 (41)
CR	6 (8)
PR	23 (33)
SD	33 (47)
PD	8 (12)
Second-line response (26 pts)	
ORR	6 (23)
CR	0
PR	6 (23)
SD	16 (62)
PD	4 (15)
Beyond second-line response (9 pts)	
ORR	2 (22)
CR	1 (11)
PR	1 (11)
SD	7 (78)
PD	0

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate.

Table 3. Side-effects related to trastuzumab administration

Types	NCI-CTC grade		
	1	2	3
Cardiac left ventricular function	6	1	–
Cardiac arrhythmia	2	–	–
Fever	4	–	–
Rash	1	–	–
Fatigue	4	–	–
Increase of bilirubin	–	–	1
Increase of liver transaminases2		–	–

2NCI-CTC, National Cancer Institute Common Toxicity Criteria.

a wide range of chemotherapy drugs, adding little the toxicity profile of chemotherapy. Discontinuation after disease progression is still standard of care, although different trials report a benefit from the treatment beyond disease progression, changing chemotherapy regimen [21,22,23].

The potential benefit in responding patients with MBC to continue trastuzumab with a new chemotherapy drug in monotherapy is a topic of great interest.

We have reported our long-term clinical experience on safety and efficacy profile of trastuzumab. Although with a limited number of patients and in a retrospective report we have no observed significant difference in (TTP) between the different lines of treatment, that should be related to the potential benefit from continued combination treatment, supported also by the clinical benefit obtained. Moreover, we have reported a CR in third line in a patient, who had obtained a SD in first line and a PR in the second. This clinical outcome is unclear, but certainly is related to the complex interactions between HER2 pathway and neoplastic cells.

Controversial is also the higher incidence of BM during trastuzumab treatment [24, 25] that should reflect the improved peripheral tumor control and patient survival and the relative lack of activity of trastuzumab on central nervous system. The incidence of BM in our patients (16%) is in the range commonly reported for breast cancer patients [25].

Prolonged administration of trastuzumab seems to be a safe approach, with manageable toxic effects. The available data indicate that often cardiotoxicity of trastuzumab therapy may reflect an exacerbation of anthracycline-induced cardiotoxicity in previous treatments [10], usually not clinical relevant. The only grade 2 cardiotoxicity reported in our report was observed in a patient previously treated in metastatic setting with first-line anthracycline-based chemotherapy.

Twenty-five of our patients were heavily pretreated for metastatic disease (13 patients have also received adjuvant chemotherapy), but have shown a good compliance to the treatment, confirming the good safety profile of trastuzumab.

In summary, the introduction of trastuzumab in our clinical practice has certainly revolutioned the treatment of breast cancer with the development of new active therapeutic options.

Even with the large therapeutic benefits of trastuzumab, avoiding toxic effects remains an important goal and physicians must be vigilant in managing toxic effects and evaluating potential benefits and risk. Further research is warranted to resolve some important controversies on its optimal use.

references

1. Bartsch R, Wenzel C, Hussian D et al. Analysis of trastuzumab and chemotherapy in advanced breast cancer after the failure of at least one earlier combination: an observational study. BMC Cancer 2006; 6: 63.
2. Burstein HJ, Kuter I, Campos SM et al. Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. J Clin Oncol 2001; 19(10): 2722–2730.
3. Tokunaga E, Oki E, Nishida K et al. Trastuzumab and breast cancer: developments and current status. Int J Clin Oncol 2006; 11(3): 199–208.
4. Pegram MD, Lopez A, Konecny G, Slamon DJ. Trastuzumab and chemotherapeutics: drug interactions and synergies. Semin Oncol 2000; 27: 21–25; 92–100.
5. Vogel CL, Cobleigh MA, Tripathy D et al. Efficacy and safety of Herceptin (trastuzumab, humanized anti-HER2 antibody) as a single agent in first-line treatment of HER2 overexpressing metastatic breast cancer (HER2+/MBC). Breast Cancer Res Treat 1998; 50: 232 (Abstr 21).
6. Baselga J, Tripathy D, Mendelsohn J et al. Phase II study of weekly intravenous recombinant humanized anti-p185^{HER2} monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. J Clin Oncol 1996; 14: 737–744.
7. Cobleigh MA, Vogel CL, Tripathy D et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999; 17: 2639–2648.
8. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344: 783–792.
9. Marty M, Cognetti F, Maraninchi D et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 2005; 23: 4265–4274.
10. Suter TM, Cook-Bruns N, Barton C. Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. Breast 2004; 13: 173–183.
11. Untch M, Eidtmann H, du Bois A et al. Cardiac safety of trastuzumab in combination with epirubicin and cyclophosphamide in women with metastatic breast cancer: results of a phase I trial. Eur J Cancer 2004; 40: 988–997.
12. Baselga J, Climent MA, Lluch A et al. Results of a phase II study of liposomal doxorubicin (Myocet) in combination with weekly paclitaxel and trastuzumab (Herceptin) in patients with HER2-positive locally advanced or metastatic breast cancer (LA/MBC). Eur J Cancer 2004; 2 ((Suppl)): 132.
13. Burstein HJ, Harris LN, Marcom PK et al. Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: multicenter phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors and cardiac surveillance algorithm. J Clin Oncol 2003; 21: 2889–2895.
14. Pegram MD, Pienkowski T, Northfelt DW et al. Results of two open-label, multicenter phase II studies of docetaxel, platinum salts, and trastuzumab in HER-2-positive advanced breast cancer. J Natl Cancer Inst 2004; 96: 759–769.
15. Robert N, Leyland-Jones B, Asmar L et al. Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER2/neu positive advanced breast cancer. Breast Cancer Res Treat 2002; 76: 37.
16. Robert N, Leyland-Jones B, Asmar L et al. Randomized phase III study of trastuzumab, paclitaxel, and carbopaltin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol 2006; 24: 2786–2792.
17. Montemurro F, Donadio M, Clavarezza M et al. Outcome of patients with HER2-positive advanced breast cancer progressing during trastuzumab-based therapy. Oncologist 2006; 11: 318–324.
18. Jackisch C. HER-2-positive metastatic breast cancer: optimizing trastuzumab-based therapy. Oncologist 2006; 11 (Suppl 1): 34–41.
19. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92(3): 205–216.
20. Trotti A, Byhardt R, Stetz J et al. Common toxicity criteria: version 2.0 an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys 2000; 47: 13–47.
21. Gelmon KA, Mackey J, Verma S et al. Use of trastuzumab beyond disease progression: observations from a retrospective review of case histories. Clin Breast Cancer 2004; 5: 52–58.

22. Fountzilas G, Razis E, Tsavdaridis D et al. Continuation of trastuzumab beyond disease progression is feasible and safe in patients with metastatic breast cancer: a retrospective analysis of 80 cases by the Hellenic Cooperative Oncology Group. Clin Breast Cancer 2003; 4: 120–125.
23. Tripathy D, Slamon DJ, Cobleigh M et al. Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. J Clin Oncol 2004; 22: 1063–1070.
24. Lai R, Dang CT, Malkin MG, Abrey LE. The risk of central nervous system metastases after trastuzumab therapy in patients with breast carcinoma. Cancer 2004; 101(4): 810–816.
25. Yau T, Swanton C, Chua S et al. Incidence, pattern and timing of brain metastases among patients with advanced breast cancer treated with trastuzumab. Acta Oncol 2006; 45: 196–201.