The Breast 53 (2020) 18–22

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Metronomic oral chemotherapy with cyclophosphamide plus capecitabine combined with trastuzumab (HEX) as first line therapy of HER-2 positive advanced breast cancer: A phase II trial of the Gruppo Oncologico Italia Meridionale (GOIM)

Laura Orlando [a, *], Vito Lorusso [b], Francesco Giotta [b], Massimo Di Maio [c], Paola Schiavone [a], Palma Fedele [a], Annamaria Quaranta [a], Chiara Caliolo [a], Mariangela Ciccarese [d], Margherita Cinefra [a], Sante Romito [e], Salvatore Pisconti [f], Salvatore del Prete [g], Michele Aieta [h], Daniele Rizzi [b], Evaristo Maiello [i], Giuseppe Colucci [b], Saverio Cinieri [a], on behalf of GOIM (Gruppo Oncologico dell'Italia Meridionale)

[a] Medical Oncology, Antonio Perrino Hospital, Brindisi, Italy
[b] Medical Oncology, Istituto Tumori Giovanni Paolo II, IRCCS, Bari, Italy
[c] Department of Oncology, University of Turin at Ordine Mauriziano Hospital, Turin, Italy
[d] Medical Oncology, Ospedale Vito Fazzi, Lecce, Italy
[e] Medical Oncology, Ospedali Riuniti, Foggia, Italy
[f] Medical Oncology, Ospedale Moscato, Taranto, Italy
[g] Medical Oncology, Ospedale San Giovanni di Dio, Frattamaggiore, Napoli, Italy
[h] Medical Oncology, Ospedale Oncologico Regionale, Rionero in Vulture, Potenza, Italy
[i] Medical Oncology, Ospedale Sollievo Della Sofferenza, IRCCS, San Giovanni Rotondo, Foggia, Italy

ARTICLE INFO

Article history:
Received 9 February 2020
Received in revised form
26 May 2020
Accepted 2 June 2020
Available online 5 June 2020

Keywords:
HER-2 positive
Metronomic chemotherapy
Advanced breast cancer

ABSTRACT

Background. The combination of chemotherapy plus anti HER-2 agents is the mainstay of HER-2 positive advanced breast cancer (ABC) therapy. We conducted a phase II trial testing activity and safety of trastuzumab and metronomic capecitabine/cyclophosphamide (HEX) as first-line therapy in HER-2 positive ABC.

Methods. Patients at first relapse or with synchronous metastasis were treated with trastuzumab (4 mg/kg, biweekly) plus oral capecitabine (1500 mg/daily) and cyclophosphamide (50 mg/daily). Primary endpoint was objective response rate (ORR), secondary endpoints progression-free survival (PFS), clinical benefit rate (CBR; PR + CR + SD for $\geq$ 24 weeks) and tolerability. Optimal two-stage design was applied. Results. Sixty patients with measurable ABC, tumors scored as +3 for HER-2 or FISH +, untreated for advanced disease were enrolled. Median age was 62.5 years, visceral metastases were present in most patients (57.9%). Median number of cycles was 16 (range 1–98). ORR was 56.7% (95% CI, 44.1–68.4%), with 5 CR (8.3%) and 29 PR (48.3%). Fifteen patients had SD (25%). The CBR was 78.2%. Nine progressions were observed (15%). Median PFS was 11 months. One year PFS was 47.7%. Median OS was 45.9 months. Worst toxicities were grade 3 hand-foot syndrome in 2 pts (3.3%), grade 3 anaemia in 2 pts (3.3%), grade 2 nausea in 2 pts (3.3%) and grade 3–4 diarrhea in 2 pts (3.3%). Cardiac toxicity grade 1 was reported in 1 pt. Conclusions. Combination of trastuzumab and metronomic oral chemotherapy has clinical activity. The tolerability was excellent and allowed the prolonged delivery of treatment.

* Corresponding author. Oncology Division & Breast Unit, Antonio Perrino Hospital, 72100, Brindisi, Strada Statale 7 (Via Appia), Italy.
E-mail addresses: laura.orlando68@gmail.com, onco.brindisi@gmail.com (L. Orlando).

https://doi.org/10.1016/j.breast.2020.06.002

1. Introduction

Breast cancer is the leading cause of cancer death in women [1].

Although treatable, metastatic breast cancer MBC remains an incurable disease with a median overall survival (OS) of about 3 years and a 5-year survival of about only 25% [2]. Breast cancer with gene amplification or overexpression of human epidermal growth factor receptor 2 (HER-2) encountered for 20% of all breast cancer [3]. Many studies revealed that the advances in HER-2 positive ABC therapies increased the survival time for patients with HER-2 positive breast cancer [4].

Trastuzumab was the first humanized monoclonal antibody against HER-2 to be approved as adjuvant and palliative therapy for breast cancer in combination with chemotherapy [5]. Despite the efficacy of trastuzumab, recurrences do occur and are a serious clinical problem for HER-2 positive patients
[6]. The need of overcoming trastuzumab resistance has led to the development of new therapies directed at HER-2. Pertuzumab is a humanized monoclonal antibody which prevents the dimerization of HER-2 to HER-3 (human epidermal growth factor receptor 3) [7]. Combined with trastuzumab and docetaxel, Pertuzumab has shown a significant and prolonged progression-free survival and overall survival compared to trastuzumab and docetaxel as first line therapy of HER-2 positive ABC [8,9]. Nowadays, this combination is approved as first line therapy and represents the standard of care for HER-2 positive ABC. Metastatic breast cancer is an incurable disease and the goals of therapies are mostly palliative. The maintenance of a good performance status is the consequence of both symptoms palliation and avoidance of side effects of systemic therapy. The term 'metronomic' chemotherapy (MTC) refers to the frequent, even daily administration of chemotherapeutics at doses significantly below the maximum tolerated dose, with no prolonged drug-free breaks [10]. It also defines a novel target of antitumor therapies. Preclinical studies have identified the tumor endothelial cell as the main target of MTC, but others mechanisms of action operating in MTC, such as stimulation of immune response, circulating endothelial cells (CECs) inhibition and direct action on tumor cells have been described too [11].

In a previous small series, low-dose oral cyclophosphamide and methotrexate combined with trastuzumab have shown substantial efficacy in metastatic HER-2 positive breast cancer and provided disease control in a significant proportion of patients. The observed clinical benefit (RP plus RC plus SD for $\geq$ 24 weeks) in all patients and in patients with disease resistant to previous trastuzumab therapy was 46% (95% CI, 24–68%) and 27% (95% CI, 6–61%), respectively [12]. Data from a phase II trial with the combination of metronomic capecitabine plus cyclophosphamide regimen plus bevacizumab (a humanized monoclonal antibody against vascular endothelial growth factor, VEGF) have shown a high clinical benefit rate in untreated breast cancer patients [13].

In the present study we assessed the activity and tolerability of a new metronomic regimen with cyclophosphamide plus capecitabine in combination with trastuzumab in HER-2 positive untreated metastatic breast cancer patients.

2. Patients and methods

2.1. Study design

This phase II study was designed according to an optimal two-stage design to test the null hypothesis that p0 $\leq$ 0.4 vs. the alternative that p1 $\geq$ 0.6 with $\alpha = 0.05$ e $\beta = 0.1$ [14]. According to the original design, after testing the regimen on 25 patients in the first stage, the trial would have been terminated if 11 or fewer responses were documented. Conversely, the continuation to the second stage implied to enroll a total of 66 patients. According to the study design, study regimen should be considered active if the total number responding is higher than 32 out of 66 evaluable patients.

Primary end-point was the objective response rate (ORR), secondary end-point were the progression-free survival (PFS), the clinical benefit rate (CBR; partial response (PR)+ complete response (CR) + prolonged stable disease (SD) for $\geq$ 24 weeks) and the tolerability.

The trial was approved by each local Ethic Committee (EUDRACT 2009-017,083-16).

2.2. Patients

Eligible patients had unresectable locally recurrent or metastatic HER-2 positive breast cancer, defined by immunohistochemistry (staining 3+) or by fluorescence in situ hybridization (amplification $\geq$ 2.0), not previously treated for advanced disease. Informed Consent was signed by all patients.

2.3. Procedures

Women with histologically proven, locally advanced (inoperable) or metastatic breast untreated carcinoma were eligible. The presence of measurable disease was required. Primary and/or adjuvant chemotherapy was allowed, as well as prior endocrine treatment for any setting; prior primary and/or adjuvant trastuzumab therapy was also allowed, if ended 6 months before.

Patient eligibility criteria had to include HER-2 positivity defined according to the ASCO/CAP scoring system (at first, 2007 version and subsequently 2013 version) [4,15]: intense circumferential membrane staining in >10% of tumor cells by IHC or *HER-2* gene copy number/CEP17 signals $\geq$2 by FISH). IHC for ER (Estrogen receptor) and PgR (Progesteron receptor) was defined positive if $\geq$ 1% immune-stained tumor cells were detected.

2.4. Treatment schedule

Patients received Trastuzumab at the dose of 4 mg/kg by intravenous infusion every 14 days (loading dose at first administration 6 mg/kg), oral cyclophosphamide 50 mg daily and oral capecitabine 500 mg three times a day continuously. Every cycle started with each administration of Trastuzumab. Endocrine therapy for endocrine-responsive disease was not admitted during study treatment.

2.5. Assessment

The response and progression were evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Patients were tested for response every 8 weeks (every 4 weeks for superficial lesions) by CT scan or MRI. In addition, confirmatory scans should also be obtained not more than 4 weeks following initial documentation of objective response.

Adverse events were evaluated according to the Common Terminology Criteria for Adverse Effects Version 4.0 (CTCAE 4.0). Complete blood sample including serum hematology and biochemistry was collected every 4 weeks; serum hematology was performed also at each cycle (every 14 days).

All patients had left ventricular ejection fraction (LVEF) measurement of at least 50% by echocardiography or MUGA scan. Subsequent scheduled LVEF assessments were performed every 3 months during treatment and every 6 months during follow-up.

3. Results

From November 2011 to September 2015, 60 patients were enrolled. The median age was 62.5 years (range 32–87). Median DFI (disease-free interval) was 41 months (range 5–252). Main patients' features are summarized in Table 1. Seventeen patients (28.3%) were treated with adjuvant trastuzumab; visceral metastases were present in 33 patients (55%), liver in 22 (36.6%). The majority had 2 or more sites of recurrence. Hormone receptors were positive in 44 patients (73.3%). Median number of administered cycles was 16 (range 1–98) and median treatment duration was 7.6 months.

3.1. Efficacy

At a median follow-up of 45.7 months, 34 out of 60 patients obtained an objective response, corresponding to an ORR equal to 56.7% (95% CI, 44.1–68.4%), with 5 CR (8.3%) and 29 PR (48.3%). Consequently, even if the total sample size planned (66 patients) was not reached, the minimum number of 33 objective responses needed to define the study treatment as active was reached in the first 60 patients.

15 patients had SD (25%). The CBR was 78.2%. Nine progressions were observed (15%). (Table 2). Median PFS was 11 months (95% CI, 6.3–15.6) (Fig. 1A). One year PFS was 47.7%. Median OS was 45.9 months (95% CI, 22.7–69.1) (Fig. 1B).

3.2. Toxicity

The most commonly reported toxicities were G1 events: thrombocytopenia (8 patients, 13.3%), hand-foot syndrome (11 patients, 18.3%), nausea (7 patients 11.7%), diarrhea (8 patients, 13.3%), fever (8 patients, 13.3%). Other toxicities were: anemia G3 (2 patients, 3.3%), hand-foot syndrome G3 (2 patients, 3.3%), diarrhea G3-G4 (2 patients, 3.3%) (Table 3). Cardiac toxicity G1 was observed in 1 patient (1.6%). Alopecia was not reported.

One patient (1.6%) discontinued treatment because of diarrhea G4 after one cycle; treatment delays were not reported.

Table 1
Main patients' features.

Age (median)	62.5 (32–87)
Menopausal status: pre (%)	9 (15%)
Post (%)	51 (85%)
Hormonal receptor status: pos	44 (73.3%)
neg	16 (26.6%)
Metastasis: synchronous	22 (38.6%)
metachronous	35 (61.4)
DFI (median, range)[a]	41 (5–252)
Previous CT	28 (46.6%)
Previous Trastuzumab	17 (28.3%)
Visceral sites	33 (55%)
Liver metastases	22 (36.6%)
N° sites ≥ 2	49 (81.6%)

[a] In 35 pts with metachronous metastasis.

Table 2
Clinical results at median follow up of 45.7 months.

Pts	60
RC	5 (8.3)
RP	29 (48.3%)
ORR	34 (56.7%)
SD	15 (25%)
OCB[a]	47 (78.2%)
PD	9 (15%)

[a] OCB: overall clinical benefit defined as PR + CR + SD for ≥ 24 weeks.

4. Discussion

In this study of metronomic oral chemotherapy and antiHER-2 therapy with trastuzumab, 34 out of 60 patients had response to treatment, with ORR of 56.7% (95% CI, 44.1–68.4%) and PFS of 11 months (95% CI, 6.3–15.6), thus meeting the primary endpoint. When our trial was designed and conducted, pertuzumab in combination with trastuzumab and chemotherapy had not been approved yet. Data from Cleopatra study were impressive: the difference in PFS between pertuzumab/trastuzumab combination and trastuzumab alone was significant (HR 0.69) and the combination led to an improvement of survival by 6.3 months [8,9]. As a consequence, we stopped the accrual at 60 patients for the slowdown in the recruitment after Cleopatra data. However, even if the total sample size planned (66 patients) was not reached, the minimum number of 33 objective responses needed to define the study treatment as active was reached even in the first 60 patients.

In our study, median OS was 45.9 months, the probability to survive at 12 and 24 months was 93.1% and 79.6% respectively. Our data compared favorably with data from HERNATA trial, a phase III trial comparing vinorelbine and docetaxel associated with trastuzumab as first line therapy for HER-2 positive ABC. In this trial, TTP for docetaxel and vinorelbine was 12.4 months and 15.3 months respectively, the median overall survival was 35.7 months versus 38.8 months and the 1-year survival rate was 88% in both arms [16].

Unlike Cleopatra and HERNATA trials, in which only 10% and 0.4% of patients had received adjuvant trastuzumab respectively, 28.3% of our patients were treated with trastuzumab in the adjuvant setting. This point might define our population as more resistant, despite the fact that the majority of patients enrolled in our trial had a long DFI.

Trastuzumab given with metronomic oral chemotherapy was well tolerated. Grade 3 and 4 toxicities were rare. Neither alopecia nor significant cardiac toxicity were reported.

The opportunity to continue treatment, without cumulative toxicity and good tolerability is a main issue in palliative setting. The use of metronomic delivery could improve the therapeutic index of drugs by optimally balancing activity and treatment associated toxicities, thus allowing prolonged duration of treatment and ensuring clinical benefit. In our study, median number of administered cycles was 16 (range 1–98). Seven women received more than 50 courses; at the time of analysis, 1 patient was still free of progression after 98 cycles. Despite this prolonged administration, cumulative toxicity was not reported, as it is predictable and desirable with metronomic schedule.

Nowadays, most efforts are aimed at discovering novel combinations (or indications) in the early stage breast cancer. Pertuzumab was recently approved by FDA in both adjuvant and neoadjuvant setting for HER-2 positive tumors [18].

Moreover, trastuzumab emtansine has newly shown to reduce the risk of invasive disease recurrence or death by 50% compared with trastuzumab in patients with residual invasive tumor in breast or axillary nodes at surgery after completing neoadjuvant trastuzumab-chemotherapy [19].

The currently empowering of systemic treatment pursued by trials conducted in early breast cancer will conduct to an increasing number of advanced breast cancer patients pre-treated with therapies directed against HER-2 protein, for whom different therapeutic approach are needed in the metastatic setting.

Nowadays, underlying mechanisms of HER-2 therapy resistance

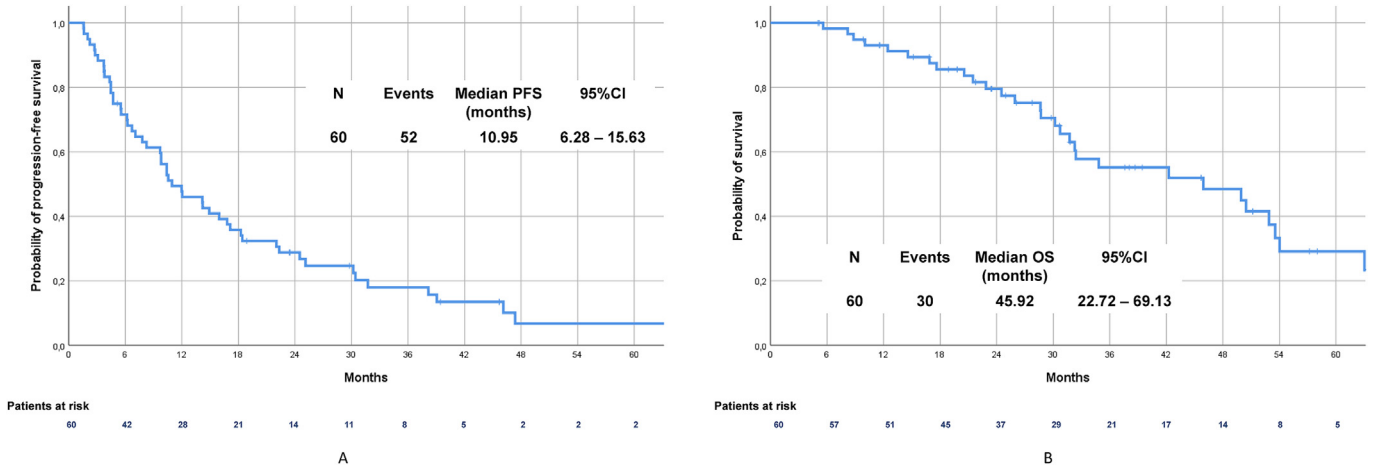

Fig. 1. A. Progression-free survival in the study population, B. Overall survival in the study population.

Table 3
Treatment toxicity.

	All grades (%)	G3 (%)	G4 (%)
Anemia	15 (25)	2 (3.3)	–
Thrombocytopenia	9 (15)	–	–
Neutropenia	5 (8.3)	–	–
Liver toxicity	5 (8.3)	–	–
Fever	8 (13.3)	–	–
HF Syndrome[a]	13 (21.7)	2 (3.3)	–
Asthenia	5 (8.3)	–	–
Nausea	9 (15)	–	–
Diarrhea	10 (16.7)	1 (1.7)	1 (1.7)
Renal toxicity	3 (5.0)	–	–
Stomatitis	2 (3.3)	–	–
Myalgias	3 (5.0)	–	–
Arthalgias	2 (3.3)	–	–

[a] Hand-foot syndrome.

are better understood, and novel combined targeted therapies are under investigation. The introduction of vaccines, antibody drug conjugate and bifunctional antibodies will probably make less exciting the trastuzumab/chemotherapy combination [20,21]. However, the availability of further, low-toxic association of "old" cytotoxic and antiHER-2 agents could be useful to obtain a disease control and to maintain a good quality of life also in subsequent line of treatment.

Our data, because of the scant number of patients, do not allow to define a subpopulation that benefit the most from metronomic combination.

We observed a low percentage of objective responses and a greater number of PD in hormone receptor negative patients compared to hormone receptor positive (50% vs 61% respectively and 18% vs 13% respectively, data not shown), but these data are insufficient to define a more responsive population.

The majority of our patients developed metastatic recurrence after a long DFI (median 41, range 5–252). Despite that, the median overall survival of 45.9 months probably does not reflect a favorable prognostic profile; however, all the CR were observed in patients with DFI longer than 10 years or with de novo metastatic disease (data not shown).

The possibility to selected other chemotherapeutic agents to be used in combination with pertuzumab and trastuzumab is under investigation. Eribulin, vinorelbine or capecitabine were studied as the first line therapy for metastatic or recurrent cancer, with promising efficacy [22].

Recently, the activity of dual antiHER-2 treatment with or without metronomic chemotherapy was evaluated in older and frail patients with HER-2 positive metastatic breast cancer. Eighty patients, of whom 56 (70%) had a potential frailty profile according to the geriatric screening G8 score, were randomly assigned to receive trastuzumab and pertuzumab (n = 39) or trastuzumab and pertuzumab plus metronomic oral cyclophosphamide (n = 41). At a median follow-up of 20.7 months, the median progression-free survival was 5.6 months with trastuzumab and pertuzumab versus 12.7 months with the addition of metronomic oral cyclophosphamide [23].

Based on our results, a trial comparing metronomic chemotherapy plus trastuzumab and pertuzumab versus standard combinations could be desirable, mainly in specific subpopulations, such as elderly or frail ABC patients.

The palliative purpose of treatment in ABC together with symptoms control and maintenance of quality of life are desirable therapy end-points
[2]. In our study, a systematic evaluation of quality of life through Patient-Reported Outcome Measures has not be scheduled, thus partially invalidating the potential value of our schedule. The good tolerability resulted in satisfying patients' health status reported on the majority of medical records cannot be considered *per se* a surrogate of Health-Related Quality of Life (HRQoL), a crucial endpoint of new therapeutic interventions.

In our trial, trastuzumab was delivered as biweekly schedule, based on our previous work in which biweekly administration of chemotherapy and trastuzumab was thought to be safer and better tolerated than standard schedule [17]. Although the hypothesis of an antiangiogenic effect due to frequent administration of chemotherapy probably finds no basis with antiHER-2 therapies, we decided to maintain the biweekly administration of trastuzumab with metronomic chemotherapy, considering also the data of an increased cardiac toxicity with schedule administered every 3 weeks [24].

In our study, the common RECIST 1.1 criteria were adopted to evaluate tumor response. The classical tumor size measurements are probably not adequate to evaluate activity of metronomic chemotherapy. Data from a retrospective analysis showed how the metabolic response often precedes the anatomic response mainly in therapies including metronomic therapy. The angiogenic dormancy effect of metronomic treatment has as a consequence changes in morphologic characteristics slower than functional changes, thus it is conceivable the use of different techniques (such

as the FDG-PET) would be more appropriate [25].

Moreover, apoptotic circulating endothelial cells (CECs) have been associated to clinical benefit in many clinical trials using antiangiogenic agents [26]. Our study was not designed to correlate clinical activity and clinical benefit with surrogate markers of angiogenesis or anti-angiogenesis as previously reported in other trials with metronomic chemotherapy. It is conceivable that metronomic chemotherapy in ABC should gain value if reproducible prognostic or predictive biomarkers will be available in clinical trials.

Our results are encouraging and warrant larger controlled clinical trials designed to confirm the role of less toxic, low dose chemotherapy protocols also in HER-2 positive breast cancer, even considering that an increasing number of patients will be more deeply pre-treated in early setting with antiHER-2 therapies.

Declaration of competing interest

The authors have no conflict of interest.

References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics. CA Cancer J Clin 2013;63:11–30.
[2] Cardoso F, Senkus E, Costa A, et al. 4th ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 4 annals of. Oncology 2018;29:1634–57.
[3] Wolff A, Hammond ME, Hicks DG, et al. 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;31:3997–4013.
[4] Sundquist M, Brudin L, Tejler G. Improved survival in metastatic breast cancer 1985-2016. Breast 2017;31:46–50.
[5] Giordano SH, Temin S, Kirshner JJ, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer . American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014;32:2078–99.
[6] Andersson M, Lidbrink E, Bjerre K, et al. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. J Clin Oncol 2011;29:264–71.
[7] Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2and discovering ERBB3. Nat Rev Canc 2009;9:463–75.
[8] Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Cancer 2012;306:109–19.
[9] Swain SM, Kim SB, Cortes J, et al. Overall survival benefit with pertuzumab, trastuzumab and docetaxel for HER2-positive metastatic breast cancer in CLEOPATRA, a randomized Phase 3 study. Lancet Oncol 2013;14:461–71.
[10] Browder T, Butterfield CE, Kraling BM, Shi B, Mar- shall B, O'Reilly MS, Folkman J. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. Cancer Res 2000;60:1878–86.
[11] Hanahan D, Bergers G, Bergsland E. Less is more, regularly: metronomic dosing of cytotoxic drugs can target can target tumour angiogenesis in mice. J Clin Invest 2000;105:1045–7.
[12] Orlando L, Cardillo A, Ghisini R, et al. Trastuzumab in combination with metronomic cyclophosphamide and methotrexate in patients with Her-2 positive metastatic breast cancer. BMC Canc 2006;6:225–30.
[13] Dellapasqua S, Bertolini F, Bagnardi V, Campagnoli E, Scarano E, Torrisi R, Shaked Y, Mancuso P, Goldhirsch A, Rocca A, Pietri E. Colleoni M Metronomic cyclophosphamide and capecitabine combined with bevacizumab in advanced breast cancer. J Clin Oncol 2008;26:4899–905.
[14] Simon R. Optimal two stage designs for phase II clinical trials. Contr Clin Trials 1989;10:1–10.
[15] Wolf AC, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med 2007;31:18–43.
[16] Andersson M1, Lidbrink E, Bjerre K. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. J Clin Oncol 2011 Ja20;29(3):264–71.
[17] Orlando L, Giotta F, Lorusso V, et al. Biweekly combination of trastuzumab, docetaxel and gemcitabine for HER2-positive metastatsic breast cancer: results of a phase II GOIM study. Future Oncol 2014;10(5):725–33.
[18] von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med 2017;377:122–31.
[19] von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019;377 92:122–31.
[20] Ayoub NM, Al-Shami KM, yaghan RJ. Immunotherapy for HER2-positive breast cancer: recent advances and combination therapeutic approach]. Breast Cancer 2019;11:53–69.
[21] De Giovanni C, Nicoletti G, Quaglino E, et al. Vaccines against human HER2 prevent mammary carcinoma in mice transgenic for human HER2. Breast Cancer Res 2014;16 R10.
[22] Kei Ishii Nao Morii Hiroyasu Yamashiro Pertuzumab in the treatment of HER2-positive breast cancer: an evidence-based review of its safety, efficacy, and place in therapy. Core Evid 2019;14:51–70.
[23] Wildiers H, Tryfonidis K, Dal Lago L, et al. Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group. Lancet Oncol 2018;19(3):323–36.
[24] Genuinoa AJ, Chaikledkaewab U, Thea DO, Reungwetwattanac T, Thakkinstiana A. Adjuvant trastuzumab regimen for HER2-positive early-stage breast cancer: a systematic review and meta-analysis. Expet Rev Clin Pharmacol 2019;12(8):815–82.
[25] Agrawal A, Purandare N, Ahah S, et al. Response assessment in metronomic chemotherapy: RECIST or PERCIST? Indian J Nucl Med 2014;29(2):74–80.
[26] Mancuso P, Colleoni M, Calleri A, et al. Circulating endothelial-cell kinetics and viability predicit survival in breast cancer patients receiving metronomic chemotherapy. Blood 2006;108. 452-45.