The Breast 19 (2010) 128–132

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Preoperative therapy with trastuzumab and oral vinorelbine (± endocrine therapy) in patients with HER2-positive breast cancer

Monica Iorfida [a,i,*], Vincenzo Bagnardi [e,f,g], Alessandra Balduzzi [a,i], Silvia Dellapasqua [a,i], Anna Cardillo [a,i], Alberto Luini [d], Mattia Intra [d], Ida Minchella [h], Paolo Veronesi [d], Giuseppe Viale [b,c], Aron Goldhirsch [i], Marco Colleoni [a,i]

[a] Unit of Research in Medical Senology, European Institute of Oncology, Via Ripamonti 435, 20141, Milan, Italy
[b] Division of Pathology, European Institute of Oncology, Via Ripamonti 435, 20141, Milan, Italy
[c] University of Milan School of Medicine, Milan, Italy
[d] Division of Senology, European Institute of Oncology, Via Ripamonti 435, 20141, Milan, Italy
[e] Division of Epidemiology and Biostatistics, European Institute of Oncology, Via Ripamonti 435, 20141, Milan, Italy
[f] Department of Statistics, University of Milan-Bicocca, Milan, Italy
[g] Frontier Science and Technology Research Foundation, Southern Europe, Milan, Italy
[h] Medical Care Unit, European Institute of Oncology Milan, via Ripamonti 435, Milan 20141, Italy
[i] Department of Medicine, European Institute of Oncology Milan, via Ripamonti 435, Milan 20141, Italy

ARTICLE INFO

Article history:
Received 28 August 2009
Received in revised form
20 November 2009
Accepted 27 December 2009

Keywords:
Preoperative therapy
Trastuzumab
Oral vinorelbine
Breast cancer

ABSTRACT

Background: Combined trastuzumab and intravenous vinorelbine yielded high clinical activity as preoperative treatment in patients (pts) with HER 2/*neu* positive breast cancer.
Patients and methods: We tested a preoperative combination of trastuzumab with oral vinorelbine (oV) in pts with locally advanced (T2-T4 N0-3 M0) HER2-positive breast cancer. Trastuzumab was administered i.v q 3 wks and oV was administered at the dose of 55 mg/sqm on days 1 and 3 q 3 wks, for 8 courses. Pts with ER $\geq$ 10% tumors received endocrine therapy with letrozole 2.5 mg/day, plus monthly triptorelin if premenopausal.
Results: Forty-five pts entered the study. The overall response rate (CR + PR) was 76% (95% CI: 60%–87%). pCR was observed in 4 pts (10%). Among ER-positive tumors 21/25 pts obtained a clinical response (84%) and two pts obtained a pCR (8%).
Conclusions: The combination of trastuzumab and oral vinorelbine demonstrated encouraging activity in patients with HER 2 positive ER-positive tumors. Alternative strategies should be investigated in patients with endocrine non responsive disease.

Introduction

Substantial activity has been shown for the combination of trastuzumab and several cytotoxic agents in the preoperative setting with objective response rate ranging from 70 to 90% and pathological complete remissions (pCR) reported in 7–78%.[1]

Vinorebine is characterized by a favourable safety profile compared with other drugs showing in preclinical models synergism with trastuzumab. High clinical activity was also shown in the advanced disease [2] using the combination of weekly trastuzumab and intravenous vinorelbine. A small randomized study showed equivalent activity for vinorelbine and taxanes in combination with trastuzumab for HER2-positive advanced breast cancer.[3] When used as preoperative treatment the combination yelded a 20% of pCR rate.[4]

The oral and the i.v. formulations of vinorelbine had equivalent activity, with a better tolerance profile for the former. Chemical phlebitis is avoided, sparing the patient the implant of a central venous access. Oral vinorelbine has been routinely introduced in polychemotherapy regimens for advanced breast cancer with substantial clinical activity and high patient compliance.

In particular, the combination of 3-weekly trastuzumab and oral vinorelbine has provided a response rate ranging from 43% to 68% in HER2-positive advanced breast cancer.[5,6]

We reported the results of a prospective phase II study investigating the activity of the combination of 3-weekly trastuzumab and oral vinorelbine in patients with HER2-positive locally advanced breast cancer. Patients with estrogen receptor positive

* Corresponding author. Tel.: +39 02 57489502; fax: +39 02 94379205.
E-mail address: monica.iorfida@ieo.it (M. Iorfida).

0960-9776/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.breast.2009.12.011

disease (ER ≥ 10% of the cells) also received endocrine therapy with letrozole, in combination with ovarian suppression if premenopausal.[7]

Patients and methods

Patients with stage II-III (cT2-4a-d, N0-2, M0), HER2-positive, any ER and PgR, breast cancer consecutively admitted at the Department of Medicine of the European Institute of Oncology (EIO) from July 2004 to October 2006 were enrolled into this study. A core biopsy was performed for diagnosis and for the assessment of the biological variables of the tumor. Investigations (chest X-ray, abdomen ultrasound and bone scan) were performed to exclude distant metastasis and blood tests were performed to assess bone marrow, renal and hepatic function. Cardiac function was assessed at baseline by ECG and echocardiography. An LVEF >50% and no impairment of ventricular kinesis were required for enrolment in the study.

ER and PgR status, assessment of the proliferative fraction (% of Ki-67 stained cells) and over-expression of HER2 were determined both on core biopsies at the time of diagnosis, as previously described,[8] and on residual tumor after surgery. Steroid hormone receptors status was classified as negative (ER and PgR < 10% of the cells), or positive (ER and/or PgR ≥ 10% of the cells). The results were recorded as the percentage of immunoreactive cells over at least 2000 neoplastic cells. The value of Ki-67 labelling index was used as a cut-off in distinguishing tumors with low (<20%) and high (≥20%) proliferative fraction. The value of 20% was selected based on previous data from our group indicating that this threshold significantly correlated with higher response rate to preoperative chemotherapy.[9]

Only nuclear reactivity was taken into account for ER, PgR, and Ki-67 antigen.

HER2-positive status was defined either as the occurrence of intense and complete immunostaining in >10% of the neoplastic cells, or as gene amplification by dual color fluorescence in situ hybridization (FISH).

Immunostaining experiments for the localization of ER and PgR, HER2 protein and Ki-67 antigen were performed on consecutive tissue sections of the core biopsies obtained before primary treatment, as previously reported.[8] The following primary antibodies were used: the monoclonal antibody (MAb) to ER (clone 1D5 at 1/100 diluition, Dako, Glostrup, Denmark), the Mab to PgR (clone 1A6, 1/800, Dako), the MIB-1 Mab to the Ki-67 antigen (Dako, 1/1200), the polyclonal antiserum (Dako, 1/3200) to the HER2 protein.

Patients received a loading dose of trastuzumab 8 mg/kg as a 90′ iv infusion followed by a dose of 6 mg/kg every 3 weeks for 8 courses. Vinorelbine was administered orally at the dosage of 55 mg/sqm on day 2 and 4 of the 1st cycle and thereafter on day 1 and 3 for 8 courses, as previously reported.[6] Patients were instructed to swallow the tablets without chewing. Standard anti-hemetic premedication with oral granisetron was administered 30′ before vinorelbine.

Letrozole 2.5 mg/day was started concomitantly with chemo-immunotherapy in postmenopausal women with ER ≥ 10% tumors and after achievement of postmenopausal estradiol levels in premenopausal women with ER ≥ 10% tumors who received monthly triptorelin 3.75 mg as intramuscular injection. Estradiol levels were monitored periodically during treatment.

Patients were assessed at each course for clinical response, by physical examination with a caliper, and at baseline, at the 4th cycle and after the completion of the 8th cycle of trastuzumab and vinorelbine for instrumental response with breast ultrasound and mammography.

Clinical responses were evaluated according to both radiological (breast ultrasound or mammography) and clinical evaluation, by measuring the largest diameters of the tumor and were graded according to standard RECIST criteria.[10]

Pathological complete remissions (pCR) were evaluated according to Kuerer et al.[11] A pCR was defined as a total disappearance of invasive tumor both in the breast and in the axilla. The presence of intraductal carcinoma qualified for pCR.

Toxicity was recorded and classified according to the NCITC-CTG Criteria. The treatment was postponed by one week if the blood count on day 21 showed a neutrophil count <1000/mm3 and/or platelet count <100,000 mm^3. In case of febrile neutropenia, or anemia, mucositis, hand & foot syndrome, gastrointestinal, biochemical and neurological toxicity ≥ grade 2, dose reduction by 25% of the related drug was performed.

Surgery was performed approximately 28 days after the last cycle of chemoimmunotherapy to allow recovery from toxicity.

Written informed consent was obtained from all patients. The protocol was notified to the Ethical Committee.

The primary end point of this study was pCR rate. The secondary endpoints were the objective response rate, toxicity and disease free survival (DFS).

Confidence intervals for proportions were calculated using the normal approximation to the binomial distribution. The Fisher exact test was used to evaluate differences in the distribution of categorical variables.

DFS was defined as the length of time from the date of the start of treatment to any event such as relapse (including ipsilateral breast recurrence), appearance of a second primary cancer (including contralateral breast cancer) or death, whichever occurred first. For survivors, DFS was censored at the last follow-up visit. The DFS distribution was estimated using the Kaplan–Meier method.

All *p*-values were two sided. The statistical analyses were run using SAS version 8.2 (SAS Institute Inc, Cary, NC).

Results

From July 2004 to October 2006 forty-five patients were enrolled in a prospective study (mean age, 46 years; range 31–67 years). Patients' and tumors' characteristics are summarized in

Table 1
Characteristic at presentation.

	N	% col
Age, years		
Mean [Range]	46 [31–67]	
Menopausal status		
Premeopausal	35	78
Postmenopausal	10	22
Clinical T		
T2	24	53
T3	16	36
T4	5	11
Clinical Nodal status		
N0	2	4
N1	42	94
NX	1	2
Hormone receptor status		
ER-negative, PgR negative	20	44
ER-positive,[a] PgR negative	7	16
ER-positive,[a] PgR positive[a]	18	40
HER 2/neu status		
3+	45	100
Ki-67		
>=20%	45	100
Nuclear grade		
2	25	56
3	20	44

[a] ER ≥ 10% of the cells.