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SHORT COMMUNICATION



The trastuzumab and vinorelbine combination: an alternative to taxane-based chemotherapy for early-stage and locally advanced HER2-positive breast cancer

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ABSTRACT

Background

Anthracyclines and taxanes have historically constituted the backbone of chemotherapy regimens for patients with breast cancer positive for the human epidermal growth factor receptor 2 (HER2). For a subset of patients who categorically refuse alopecia, or for those with a contraindication to those drugs, there is an urgent need to define alternative regimens. Here, we report our institutional experience with trastuzumab and vinorelbine (TV), a combination with good clinical activity and a good side effect profile for patients with HER2-positive breast cancer.

Methods

In a retrospective analysis, outcomes data were extracted for patients receiving TV as their only chemotherapy in the non-metastatic setting at the Jewish General Hospital. For the most part, TV was administered weekly for 6 months, followed by trastuzumab for 6 months.

Results

The analysis identified 46 patients (mean age: 64 years) who received TV between 2003 and 2012 (n = 36 adjuvant, n = 10 neoadjuvant). Of the patients in the adjuvant group, 81% had stage I disease. In the neoadjuvant group, 3 patients experienced a complete pathologic response. Only 1 patient experienced local recurrence after a short course (3 months) of adjuvant TV. Overall survival and breast cancer–specific survival were 94% and 98% respectively at a median 5 years of follow-up. Febrile neutropenia–induced sepsis resulted in the death of 1 patient with significant medical comorbidities; 2 other patients died of comorbidities unrelated to their cancer or treatment. Grades 3 or 4 adverse events included neutropenia (23%), febrile neutropenia (10%), fatigue (2%), and anemia (2%).

Conclusions

For patients with non-metastatic breast cancer refusing alopecia, or for patients who are not candidates for standard chemotherapy, TV is a reasonable alternative to standard adjuvant chemotherapy.

KEY WORDS

Breast cancer, small tumours, early breast cancer, HER2-positivity, trastuzumab, Herceptin, vinorelbine, Navelbine

1. INTRODUCTION

The adjuvant use of trastuzumab, a humanized monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER2), has, across multiple major clinical trials[1–4], significantly reduced breast cancer mortality in patients harbouring HER2 amplification. In the adjuvant setting, the best evidence supports giving trastuzumab in combination with a taxane after completion of an anthracycline-based chemotherapy regimen, or together with a taxane- and platinum-based regimen for patients at risk of cardiotoxicity[4]. For the subgroup of patients who are not eligible for the foregoing regimens, either because of a preference to avoid alopecia as a potential side effect or because of advanced age and medical comorbidities, the need to develop alternative trastuzumab-based regimens remains urgent.

Historically, patients with HER2-positive tumours less than 1 cm in size have been excluded from the major trastuzumab clinical trials. Recent evidence shows that, compared with patients having HER2-negative tumours of similar size, the HER2-positive population is at higher risk of recurrence, thus explaining the increasing rate at which adjuvant chemotherapy is being used in that group[5,6]. The only randomized trials currently in progress to analyze treatment decisions in that patient population (APT and ATEMPT) use taxanes as their backbone, again limiting the alternatives for patients who often require "lighter chemotherapy."

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Vinorelbine, a vinca alkaloid drug, was shown to have good synergistic activity with trastuzumab in preclinical studies[7]. Multiple phase II trials of the trastuzumab–vinorelbine (TV) regimen in the metastatic setting have reported response rates of up to 86%, with manageable toxicity[8–11]. Two large phase III randomized trials also reported similar efficacy and favourable toxicity for the TV regimen compared with taxane-based therapy in the metastatic setting[12,13]. We previously reported the only existing data supporting the use of TV in the adjuvant and neoadjuvant setting in 28 non-metastatic breast cancer patients[14]. Here, we report updated follow-up outcomes and additional data for the TV regimen, showing good clinical activity and limited toxicity.

2. METHODS

Patients with non-metastatic breast cancer receiving TV as their only neoadjuvant or adjuvant therapy between May 2003 and December 2012 were identified by review of the oncology pharmacy database at the Jewish General Hospital.

The TV regimen was administered using either 21-day cycles (trastuzumab 8 mg/kg loading dose, then 6 mg/kg on day 1; vinorelbine 25–30 mg/m^2 starting dose on days 1 and 8) or 28-day cycles (trastuzumab 4 mg/kg loading dose, then 2 mg/kg weekly; vinorelbine 25–30 mg/m^2 starting dose on days 1, 8, and 15). Patients received 6–8 cycles (6 months total) of TV, followed by single-agent trastuzumab for 6 more months. Efficacy was evaluated by overall survival and breast cancer–specific survival.

Per guidelines, patients underwent multigated acquisition imaging (or echocardiography) at baseline and approximately every 3 months during treatment.

3. RESULTS

3.1 Patient Population

Between 2003 and 2012, 46 chemotherapy-naïve patients with HER2-positive stage I–III breast cancer were treated with adjuvant ($n = 36$) or neoadjuvant ($n = 10$) TV. Mean age at diagnosis was 64 years (range: 45–81 years). Of those patients, 81% had stage I disease. Table I shows the main reasons that these patients did not receive standard chemotherapy.

Table II reports tumour characteristics. All patients were HER2-positive as defined by an immunohistochemistry score of 3+ or a gene amplification ratio exceeding 2.2 on fluorescence *in situ* hybridization, or both.

3.2 Efficacy Analysis

In addition to data previously reported[14], 2 patients in the neoadjuvant setting experienced a pathologic complete response, and 2 others experienced a good partial response. All 10 patients treated in the preoperative neoadjuvant setting have remained free of disease.

TABLE I Reasons[a] for choosing trastuzumab–vinorelbine over standard treatment in 46 breast cancer patients

Reason	*Applicable (*n*)*
Previous anthracycline-based chemotherapy	4
Invasive cancer <1 cm (pT1a–b, pN0)	18
Invasive cancer 1–2 cm (pT1c, pN0), ER+ or PR+[b]	8
General frailty	11
Specific comorbidities[c]	7
Patient refusal because of side effects	11

[a] For some patients, more than one reason is applicable.
[b] Given ER+ or PR+ status, these patients opted for a less-toxic non-standard trastuzumab-based regimen with fewer side-effects, followed by hormonal therapy.
[c] Severe aortic stenosis, previous myocardial infarction, severe chronic obstructive lung disease, liver cirrhosis, poorly controlled depression, restrictive lung disease, and chronic renal failure.

ER+ = estrogen receptor–positive; PR+ = progesterone receptor–positive.

At a median follow-up of 60 months, no recurrence was observed in patients who had completed treatment. In 1 patient who received only 4 treatment cycles, local recurrence was observed after chemotherapy was stopped. After resection of the recurrent tumour, that patient completed a full course of TV and has since remained disease-free.

Three deaths have also been reported. Two deaths were unrelated to the cancer or to the TV regimen. One patient died of decompensated cirrhosis from an underlying hepatitis B infection 6 months after completion of TV, and an elderly patient died at home in unknown circumstances, with no evidence of recurrence at her last follow-up. Febrile neutropenia-induced sepsis after 1 cycle of TV resulted in the death of one 75-year-old patient with extensive comorbidities. Overall survival and breast cancer–specific survival were 94% and 98% respectively at a median 5 years of follow-up.

3.3 Treatment Completion

Three patients discontinued treatment early. One stopped because of severe anxiety related to chemotherapy administration; one with cirrhosis developed neutropenia after the 4th cycle; and one stopped after 1 cycle of TV because of grade 3 fatigue.

3.4 Treatment Tolerability

For most patients, TV was very well tolerated overall (Table III presents the side effect profile). Uncomplicated neutropenia developed in 23% of the patients, with a febrile neutropenia rate of 10%. One grade 3

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TABLE II Clinical and pathologic staging and hormone receptor status in patients receiving trastuzumab–vinorelbine

Adjuvant treatment (36 patients)			*Neoadjuvant treatment (10 patients)*				
Pathologic stage	*Pts (n)*	*ER- or PR-positive (n)*	*Clinical stage*	*Pts (n)*	*Pathologic stage*	*Pts (n)*	*ER- or PR-positive*
Stage IA			Stage IIB		Stage IA		
T1a N0	8	4 of 8	cT2 cN1	3	ypT1a ypN0	1	0 of 1
T1b N0	10	4 of 10					
T1c N0	11	8 of 11					
Stage IIA			Stage IIIA		Stage IIA		
T1 N1	2	2 of 2	cT3 cN1	3	ypT0 ypN1	1	1 of 1
T2 N0	5	5 of 5	cT3 cN2	1	ypT1 ypN1	1	1 of 1
					ypT2 ypN0	1	1 of 1
			Stage IIIB				
			cT4 cN1	1	Stage IIB		
			cT4 cN2	2	ypT2 ypN1	1	1 of 1
					Stage IIIA		
					ypT3 ypN1	2	1 of 2
					pCR[a]	3	0 of 3

Pts = patients; ER = estrogen receptor; PR = progesterone receptor; pCR = pathologic complete response.

TABLE III Adverse events reported for the trastuzumab–vinorelbine regimen by the treating physician

Event	*Rate (%) by grade*	
	1–2	*3–4*
Neutropenia		
Uncomplicated		23
Febrile		10
Anemia		2
Fatigue	25	2
Diarrhea	15	
Nausea	8	
Dyspepsia	6	
Rash	6	
Myalgia	6	
Neuropathy	6	
Decreased LVEF	4	
Decreased appetite	4	
Vomiting	4	
Stomatitis	2	
Weight loss	2	
Cough	2	
Edema	2	
Increased bilirubin	2	
Increased transaminases	2	

LVEF = left ventricular ejection fraction.

anemia required blood transfusion, and one grade 3 fatigue resulted in discontinuation of treatment. The most frequently reported grades 1 and 2 adverse effects were fatigue and gastrointestinal toxicity.

3.5 Cardiac Safety

Patients were followed with regular multigated acquisition imaging while on treatment, and 65% underwent repeat imaging more than 1 year after completion of trastuzumab. One patient developed atrial fibrillation and clinical congestive heart failure [without a decrease in left ventricular ejection fraction (LVEF)], and trastuzumab was therefore discontinued. One patient developed an asymptomatic drop in LVEF to 43% from 51%, and her last scheduled dose of trastuzumab was therefore omitted. Her LVEF recovered to baseline on further follow-up. In one patient, no change in a borderline baseline LVEF (45%) was noted on repeat imaging.

4. DISCUSSION

Here, we report favourable outcomes of TV in two subsets of non-metastatic breast cancer patients: patients with a preference to avoid alopecia or with a contraindication to standard adjuvant chemotherapy, and patients with early-stage breast cancer for whom no standard treatment is currently defined.

Data about the use of adjuvant chemotherapy in patients with stage I HER2-positive breast cancer

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have sharply increased in the past few years from cancer centres participating in the U.S. National Comprehensive Cancer Network[6]. Two major trials are currently assessing the optimal role for adjuvant chemotherapy in that setting. In the APT trial, 406 patients with node-negative, HER2-positive tumours less than 3 cm in size were treated with weekly paclitaxel plus trastuzumab for 12 weeks, and then with every-3-weeks trastuzumab for 9 months. Recently presented early study results showed 98.7% disease-free survival at 3 years of follow-up[15]. The most common grade 3 or 4 adverse events were neutropenia (5% of patients) and neuropathy (3% of patients). On the other hand, the ATEMPT trial (search for NCT01853748 at http://clinicaltrials.gov/) is currently recruiting patients to assess the efficacy of adjuvant trastuzumab emtansine compared with paclitaxel–trastuzumab for stage I HER2-positive breast cancer. Given that both trials use taxane in their regimens, no currently known alternative is available for patients with a contraindication to that class of medications.

In two major randomized phase III clinical trials involving patients with metastatic HER2-positive breast cancer, the TV regimen was shown to have good clinical activity and a favourable side effect profile[12,13]. Results from the HERNATA study, a randomized phase III clinical trial of TV versus trastuzumab–docetaxel as first-line therapy for patients with metastatic breast cancer, showed similar efficacy for the two regimens, but with significantly fewer grades 3 and 4 toxicities in the TV treatment arm. Similar efficacy and toxicity results were obtained in the TRAVIOTA phase III randomized trial comparing TV with trastuzumab–docetaxel in the metastatic setting.

To our knowledge, our report is the only one to support the use of TV in the non-metastatic cancer setting. Despite its small sample size and retrospective nature, our institutional experience with TV suggests good clinical activity, with only 1 documented relapse case in our patient population. The TV regimen has a favourable toxicity profile, with only 3 cases of grade 3 or 4 toxicity resulting in premature discontinuation of therapy. Cardiotoxicity was also limited, with only 2 documented cases of an asymptomatic drop in LVEF. Notably, given the retrospective nature of the study, grades 1 and 2 adverse events might potentially be underreported because of a lack of efficient documentation by the treating physician.

5. CONCLUSIONS

Our study suggests that TV has activity in non-metastatic breast cancer and that it could be a reasonable alternative to standard chemotherapy for a very select population—most particularly, patients who categorically refuse alopecia. Further results from well-conducted randomized trials are required to establish a clear role for TV as a standard of care in the adjuvant and neoadjuvant setting for HER2-positive breast cancer, especially in patients with small tumours.

6. CONFLICT OF INTEREST DISCLOSURES

No author has a financial conflict of interest to declare.

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