RESEARCH ARTICLE

Safety Assessment of Intravenous Administration of Trastuzumab in 100ml Saline for the Treatment of HER2-Positive Breast Cancer Patients

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Abstract

Background: The infusion rate is considered to affect incidence and severity of infusion reactions (IRs) caused by protein formulations. Trastuzumab (TRS) is approved for 90-minute infusion as the initial dose followed by 30-minute infusion with 250 ml saline. In the study, we evaluated the safety of TRS intravenously administered over 30 minutes with 100 ml saline to reduce burden of patients, safety of infusion with 250 ml saline already being established. Materials and Methods: Women with HER2 positive breast cancer, ≥18 years and ≥55% left ventricular ejection fraction (LVEF), were registered in the study. Patients received 8mg/kg of TRS 250 ml over 90 minutes followed by 6mg/kg of TRS 100ml over 30 minutes in a three-week cycle. Results: A total of 31 patients were recruited, 24 for adjuvant therapy and seven with metastases. The median age was 59 years (range 39 to 82). The total number of TRS doses ranged from 5 to 17 with the median of 15. Mild IR occurred in two patients at the first dose. However, no IR was observed after reducing to 100 ml saline. No decrease of LVEF, increase of serum brain natriuretic peptide or any other adverse events were reported. Conclusions: Intravenous infusion of TRS with 100 ml saline over 30 minutes in breast cancer patients can be considered safe based on results from the study. It can be given on an outpatient basis as with the currently recommended dilution in 250 ml saline.

Keywords: Trastuzumab - infusion reaction - breast cancer - 100 ml saline

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Introduction

Amplification of the human epidermal growth factor receptor 2 (HER2)/neu gene is found in 20-30% of breast cancer patients (Owens et al., 2004). HER2/neu gene amplification leads to overexpression of transmembrane proteins that belong to the EGFR family and have tyrosine kinase activity. Overexpression of HER2 protein can be confirmed by immunohistochemistry (IHC) and HER2 gene amplification can be confirmed by the fluorescence in situ hybridization (FISH) method. The prognosis is poor in HER2-positive breast cancer (Slamon et al., 1987). Trastuzumab (TRS) is an anti-HER2 monoclonal antibody; protein formulation inhibits HER2 signalling by binding to HER2 proteins. Frequently reported adverse events of TRS are cardiac dysfunction and infusion reactions (Leyland-Jones et al., 2003). It is believed that the frequency and severity of infusion reactions caused by infusion of protein formulations are related to the rate of infusion (Lenz, 2007). Approved dosage of TRS is infusion with 250 ml saline over 90 minutes in Japan. Results from the ToGA (Trastuzumab for Gastric Cancer) study (Bang et al., 2010) confirmed safety of TRS infusion over 30 minutes from the second dose. In Japan, the 30 minutes infusion of TRS from the second dose was approved for both gastric cancer and breast cancer at the time of approval in gastric cancer in March 2011. Safety of the TRS 30-minute infusion from the second dose in patients with breast cancer was evaluated in the following overseas studies: a phase III clinical trial for metastatic breast cancer and NSABP B-31 study (Tan-Chiu et al., 2005), NCCTG N9831 study (Halyard et al., 2009) and BCIRG006 study (Slamon et al., 2011) for adjuvant breast cancer. Results from the studies showed safety of the infusion time reduced to 30 minutes. The currently approved dosage of TRS 30-minute infusion is TRS with 250 ml saline. The infusion time reduced by 60 minutes with the same volume of saline increases rate of infusion and it is often a concern for safety. TRS is approved for two administration schedules in Japan: 4 mg/kg as the initial dose followed by 2 mg/kg/week or 8 mg/kg as the initial dose followed by 6 mg/kg/3 weeks. The ratio of TRS in saline is not considered to affect efficacy or safety since TRS ranging from 2 mg/kg to 8 mg/kg has been administered with 250 ml saline in clinical practice. TRS infusion over 30 minutes could be given to patients with less safety concern if infusion of TRS with 100 ml

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saline is approved. Reduced infusion time per hospital visit will improve patients' quality of life. In our study, we investigated safety of TRS infusion with 100 ml saline in patients with HER2 positive breast cancer.

Materials and Methods

In the study, women with HER2 positive breast cancer were registered. IHC score of 3+ or FISH positive was considered as HER2 positive. Included patients were histologically confirmed as having invasive breast cancer, ≥18 years, Eastern Cooperative Oncology Group Performance Status 0 to 1, baseline left ventricular ejection fraction ≥55% measured by echocardiography or multi-gated acquisition scan and with written informed consent. Patients excluded from the study had inflammatory breast cancer, had serious underlying diseases, were pregnant or lactating, had cumulatively received over 360 mg/m^2 of doxorubicin or 720 mg/m^2 of epirubicin or excluded based on decision of the attending physician.

Treated patients were given TRS in three-week cycle. As the initial dose, patients received 8 mg/kg body weight of TRS reconstituted with sterile water and diluted in 250 ml saline intravenously over 90 minutes. As the subsequent doses, patients received 6 mg/kg body weight of TRS in 100 ml saline over 30 minutes if no safety signal was detected after the initial dose (Figure 1). In combination with chemotherapies, TRS was administered first. Chemotherapies were administered after evaluating safety of patients including clinical values. Basically, concurrent administration with anthracyclines including doxorubicin and epirubicin was not allowed since increased cardiovascular risk was suggested from the past reports (Slamon et al., 2001). If administration of the second dose was delayed by less than one week from the planned date, 6 mg/kg of TRS infusion over 30 minutes was allowed as the subsequent dose. However, 8 mg/kg of TRS infusion over 90 minutes was administered as the subsequent dose as same as the initial dose if the delay is longer than one week. Administration of 6 mg/kg TRS infusion over 30 minutes was allowed from the next cycle. The left ventricular ejection fraction (LVEF) was measured by echocardiography once in three months during the study. Interruption of treatments was decided according to the cardiac function algorithm of HERA study (Suter et al., 2007). Administration of TRS was immediately suspended at the occurrence of infusion reactions including fever, chills, nausea, dizziness and rash occurred within 24 hours of administration. Patients who experienced infusion reactions were treated with antihistamine agents. Infusion was resumed with reduced infusion rate after the symptoms disappeared.

The primary endpoint of this study was the incidence of infusion reactions, measured from the second dose of TRS. Secondary endpoints were as follows: incidence of adverse events after the second TRS administration; effects on cardiac function (duration and frequency of cardiac dysfunction); incidence of adverse events including infusion reaction during the first dose of TRS; and incidence of other adverse events. The adverse events evaluations were based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE ver 3.0) (Trotti et al., 2003). Patients who participated in other clinical trials were excluded. The institutional review board approved the protocol, and written informed consent was obtained for all patients.

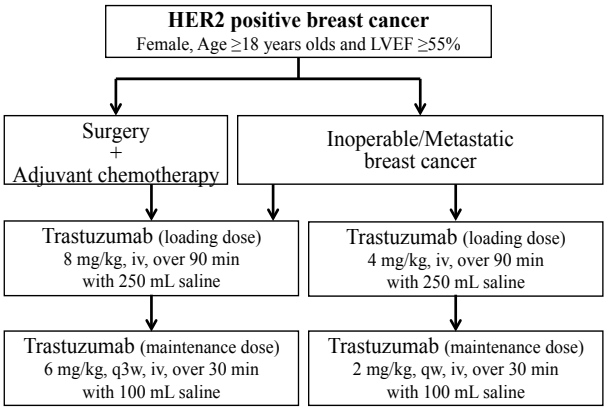

Figure 1. Treatment Flow

Results

Between June 2011 and June 2012, a total of 31 breast cancer patients were registered (Table 1). The patients were confirmed as HER2 positive breast cancer confirmed by IHC. The age of the patients ranged from 39-82 years (median 59 years). The number of patients received the study treatment as adjuvant therapy was 24 (77%): 11 patients with Stage I disease, 11 patients with

Table 1. Patients' Characteristics

Characteristic			%
No. of patients		31	
Age (years)	Median	59	
	Range	39-82	
Adjuvant		24	77
Stage	I/IIA/IIB	11/2/11	
Metastatic		7	23
Site	Lung	3	
	Liver	1	
	Bone	2	
	Others	1	
Estrogen receptor status	Positive	18	58
	Negative	9	29
	Unknown	4	13
Previous anthracycline		7	23
Previous radiotherapy		14	45

Table 2. Adverse Events

Type of response	No.	%
Any	1	3
Any-treatment related	0	0
Pain	0	0
Asthenia	0	0
Nausea/Vomiting	0	0
Fever	0	0
Chills	0	0
Rash	1	3
Peripheral edema	0	0
Dyspnea	0	0
Infection	0	0

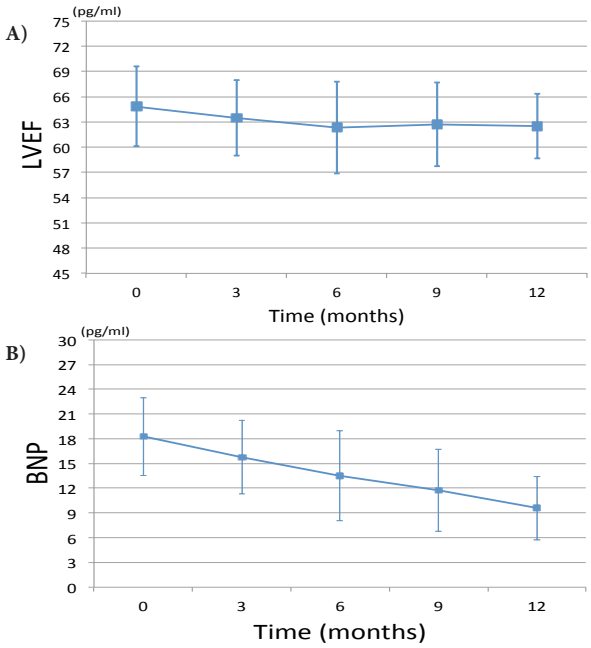

Figure 2. Time-Dependent Change. A) Left ventricular ejection fraction (LVEF: left ventricular ejection fraction) and **B)** Brain natriuretic peptide (BNP: brain natriuretic peptide)

Stage II disease, and two patients with Stage III disease. Seven patients had recurrent disease (23%): three patients with lung metastases, one patient with liver metastases, two patients with bone metastases, and one patient with metastases in other lesion. Estrogen receptor or progesterone receptor were positive in 18 patients (58%): negative in nine patients (29%) and unknown in four patients (13%). Previous treatment with anthracyclines was reported in seven patients (23%) and radiation therapy in fourteen patients (45%). The total number of TRS doses ranged from 5 to 17 with the median of 15.

Infusion reactions of grade 2 occurred in two patients (6.5%) with the initial dose. No infusion reactions at or after the second dose was reported. Other than infusion reaction, rash occurred in one patient (3.2%) as shown in Table 2. Figure 2 shows change in LVEF with time. The average LVEF measured every 3 months was between 62.3% and 64.8%. No significant decrease in LVEF was reported with the largest decrease of 8% in one patient at the 12th month on treatment. Conversely, brain natriuretic peptide (BNP) levels tended to decrease as the number of received doses increased (Figure 3). Subgroup analyses were conducted with the followings: age groups, adjuvant vs. metastatic setting, previous anthracycline treatment, and previous radiotherapy. None of the subgroup analysis showed statistical significance.

Discussion

This was the first study to assess the safety and tolerability of TRS intravenous infusion with 100 ml saline administered over 30 minutes in breast cancer patients. Safety of the 100 ml solution same as the 250 ml solution was confirmed in the study. The primary endpoint of the study was incidence of infusion reactions. Infusion reaction is described as cytokine release syndrome on CTCAE v3.0 and is said to be caused by cytokine-releasing drugs including monoclonal antibodies. It is also considered to have relation with the rate of infusion. The symptoms are similar to those seen with an allergic or hypersensitivity reaction and occur during or immediately after administration, and it is considered to recover within 24 hours after administration. In a meta-analysis of international clinical trials in metastatic breast cancer, infusion reactions were reported in approximately 40% of patients at the time of the first dose, including 0.3% with serious infusion reactions (Cook-Bruns, 2001).

Recently, many types of antibody agents have become available including humanized antibodies, chimeric antibodies and human antibodies. However, concentration and infusion time of the drugs are different for each drug without any standards. For example, bevacizumab with 100 ml saline can be administered over 30, 60, and 90 minutes, while cetuximab 500 ml is administered over 2 hours followed by 250 ml over 60 minutes. On the other hand, antibiotics are available as kit formulations of 100 ml and recommended to be administered over 30 minutes. Based on this reason, most antibiotics are administered as 100 ml solution over 30 minutes. Originally approved dosage of TRS in metastatic breast cancer with HER2 overexpression was as the following: initial dose of 4mg/kg followed by subsequent doses of 2mg/kg as an intravenous infusion over 90 minutes once weekly. The 30 minutes infusion for subsequent doses was approved later without reduction of saline from 250 ml. Increased infusion rate due to shorter time of infusion has been a concern in clinical practice. Stability of TRS with 100 ml saline has not been reported in the past. However, stability of TRS with concentration of 21 mg/ml stored for 24 hours at 2-8°C was reported in the past based on evaluation of 60 mg and 160 mg of TSR diluted respectively in 3.0 ml and 7.2 ml of sterile water (Bardin et al., 2011). TRS is prepared only with sterile water and saline because of reported protein aggregation after dilution of TRS in 5% glucose solution. Reduced time and volume of infusion will increase quality of life especially of elderly patients who have decline in cardiac, renal and liver function. In our study, grade 1 rash in one patient was the only reported adverse event. No adverse events ≥grade 2 or infusion reactions were reported.

The incidence of breast cancer in Japan continues to increase. Outpatient chemotherapy has become the standard for breast cancer treatment because of the diagnosis procedure combination payment system and emphasis on patients' quality of life. Reduction of time per patient in chemotherapy treatment is imperative under the situation. TRS infusion over 30 minutes as the second and subsequent doses is widely accepted in Europe and the United States. Our study showed TRS infusion with 100 ml saline intravenously administered over 30 minutes can be safely used in Japanese patients. The safe treatment with shorter infusion time has benefit for both healthcare professionals and patients. It is expected to become a standard treatment protocol in the future.

Acknowledgements

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