Duration of Adjuvant Trastuzumab Treatment in Routine Practice

MAGALI MONTSERRAT1, DOMINIQUE LEVEQUE1, PHILIPPE BARTHELEMY2 and JEAN PIERRE BERGERAT2

1Pharmacy and 2Oncology, Strasbourg University Hospital, Strasbourg, France

Abstract. Background: Trastuzumab is used for the adjuvant (postoperative) treatment of (HER2)-positive early breast cancer. The duration of treatment is set at one year. The goal of our study was to examine the effective duration of trastuzumab treatment in routine clinical practice. Patients and Methods: We performed a retrospective review of all patients with early breast cancer, treated with trastuzumab at our hospital between 2005 and 2008. Data concerning patterns of use and safety were collected from patient charts and pharmacy records. Results: The cohort comprised of 96 patients, with a median age of 50 years (range=25-79 years). The majority of patients (63.5%) had node-negative disease. Besides trastuzumab, most patients underwent chemotherapy (before or after surgery). Trastuzumab was administered every three weeks and the median duration of treatment was 52 weeks (range=6-81 weeks). Only half of the patients received the monoclonal antibody for 52 weeks, 36.6% had therapy more than 52 weeks and 12.5% discontinued treatment before 52 weeks due to adverse effects (8.4%) and refusal (4.2%). Two (2.1%) patients discontinued trastuzumab therapy because of cardiotoxicity, a recognized side-effect of the monoclonal antibody. Regarding treatment durations of more than 52 weeks, 15/35 were due to the off-label use of trastuzumab in the neoadjuvant setting (before surgery). The 3-year rate of disease-free survival was 91.6%. Conclusion: Half of the patients completed the 52-week treatment of trastuzumab after surgery for early breast cancer. Trastuzumab was well-tolerated and the rate of discontinuation due to cardiotoxicity was low, compared to published results.

Trastuzumab is a monoclonal antibody used in the treatment of breast cancer overexpressing the transmembrane receptor (HER2) (also known as Neu or ERBB2). Overexpression of HER2 or amplification of the gene, which occurs in 15-25% of women with breast cancer, is associated with poor clinical outcome without specific (anti-HER2) treatment (1, 2). Trastuzumab has been approved since 2006 for the adjuvant (postoperative) treatment of HER2-positive breast cancer, based on several randomized trials (3-5). A recent (2011) meta-analysis of six trials indicated that the addition of trastuzumab to chemotherapy for one year, significantly improved disease-free survival (odds ratio, OR=0.69, 95% confidence interval (CI)=0.59-0.80, p<0.001) (6). From a pragmatic point of view, trastuzumab reduces the absolute rate of recurrence at 5 years by about 9% (from 25% to 16%) and it has been estimated in the United Sates that 2,791 patients with HER2-positive breast cancer among 29,159 (9.5% of the treated patients) per year might benefit from trastuzumab therapy (i.e. avoid recurrence at 5 years) (5, 7).

According to the official labeling, trastuzumab is given by intravenous perfusion every week or every three weeks (with a tripled dose), after surgery and chemotherapy and the duration of treatment is set at one year (thus, corresponding to 52 and 18 infusions, respectively). In clinical trials, the rate of discontinuation of trastuzumab treatment ranged between 8.5% and 31.4%, the main cause being cardiotoxicity (3, 4, 8). The incidence of drug discontinuation in routine practice (i.e. outside clinical trials) is poorly documented. An English study reported that 12% of patients (13/110) stopped the treatment before one year, including 6% (n=7) for cardiac reasons (9). A Welsh study indicated that 45/239 (19.8%) patients discontinued the one-year treatment mainly due to cardiotoxicity (33/45) (10). The major aim of the current study was to evaluate, in our center, the duration of trastuzumab treatment in patients with early breast cancer and to analyze the causes of discontinuation with regard to published results.

Patients and Methods

We performed a retrospective review of all patients with early breast cancer that have started adjuvant trastuzumab treatment between January 1, 2005 and December 31, 2008 at the University Hospital of Strasbourg (France). In France, trastuzumab was used in the adjuvant setting before the official labeling of 2006, following the presentation of the preliminary results of the pivotal trials at the 2005 American Society of Clinical Oncology meeting.

Correspondence to: D. Levêque, Pharmacy, Hôpital Hautepierre, avenue Molière, France. E-mail: dominique.leveque@chru-strasbourg.fr

Key Words: Trastuzumab, adjuvant therapy, breast cancer, duration of treatment.
Patient data were first extracted by the hospital pharmacy through electronic recording of trastuzumab administrations that is necessary in France for reimbursement. Patients with early breast cancer were then identified by two oncologists. Patients with metastatic breast cancer or patients enrolled in clinical trials were excluded. Baseline characteristics of the patients including the disease and the treatment modalities (chemotherapy, hormonotherapy, radiotherapy) were extracted from the charts. Data regarding trastuzumab administration (dosing, schedule, duration of treatment, causes of discontinuation) were collected from the prescriptions at the pharmacy and from the charts. We also report on the rate of disease-free survival at three years.

**Results**

Between January 1, 2005 and December 31, 2008, a total of 96 patients with early breast cancer had started adjuvant trastuzumab treatment. Baseline characteristics are shown in Table I. The median age was 50 years (range=25-79 years). The majority (63.5%) of patients had node-negative disease. All tumours were HER-2-positive and 58.3% were hormone receptor-positive. Forty-seven (49%) patients had small tumours (i.e. <2 cm), while 46.8% had tumours between 2 and 5 cm, and 3.1% tumors greater than 5 cm.

Nearly all patients (95.8%) were given chemotherapy before or after surgery. Out of these, 61 (63.5%) received a regimen containing an anthracycline (epirubicin) and a taxane (docetaxel or paclitaxel).

Trastuzumab was given at the recommended dosage (8 mg/kg then 6 mg/kg), every three weeks as a single agent in 45 patients and associated with taxanes during the first courses in 51 patients. The median duration of trastuzumab treatment was 52 (range=6-81) weeks. Only 49 (51%) patients underwent the full course of 52 weeks. For 12 (12.5%) patients, the treatment was discontinued before one year had passed and 35 (36.5%) patients continued trastuzumab beyond one year.

Early termination of trastuzumab treatment (i.e. before 52 weeks) was due to side-effects (n=8) including 2 cardiototoxicities and patients’ refusal (n=4). Overall, only two (2.1%) patients stopped the infusions for cardiac reasons. One patient had a symptomatic fall in left ventricular ejection fraction (>15%), occurring after the third course given with docetaxel (six weeks, the shortest treatment of our study), subsequently referred to cardiologists. The other patient had an insufficient recovery of the ejection fraction (41%) after the 10th infusion. Before the initiation of trastuzumab, she had been administered six cycles of anthracycline-based chemotherapy.

The main reason for prolonged treatment was the off-label use of trastuzumab before chemotherapy (n=15). In addition, four patients completed the planned treatment (i.e. the 18 infusions) but with delays and one patient continued the treatment due to disease progression (corresponding to the longest duration of treatment, 81 weeks). Other causes included discontinuations and reintroductions, partly related to surgery.

The 3-year rate of disease-free survival for the whole population was 91.6%.

**Discussion**

In our center, we found that 12.5% of the patients with early HER2-positive breast cancer stopped trastuzumab treatment sooner than one year. Surprisingly, only two patients among 96 discontinued for cardiac reasons. Trastuzumab use is associated with cardiac events that may
necessitate treatment discontinuation (as referred in the official labeling). The mechanism is unclear but appears to be related to the concomitant or previous use of anthracyclines (i.e. doxorubicin or epirubicin) (11). In our study, out of these two patients, one had received epirubicin while the other had not. Our results are consistent with those of other pragmatic studies except for the lower rate of discontinuation for cardiac reasons (2.1% versus 6-13.8%) (9, 10). With regard to clinical trials, the rate of discontinuation is similar to that of the HERA study (8.5%) but inferior to those of the American and French trials (25-31.4%) (3, 4, 8). Furthermore, our rate of discontinuation due to cardiac problems was lower than those of clinical trials (4.5-19.9%). Early discontinuation may theoretically result in treatment failure (i.e. recurrence) but in fact the optimal duration of treatment is unknown. The duration of one year has been arbitrarily fixed and since clinical benefit occurs with only nine weekly injections, it would be very useful to have results from trials comparing short treatments to the currently approved 52 week-therapy (12). Shorter treatments may be safer, surely less costly and more convenient for the patient. In our study, most of the patients (93/96) had received trastuzumab for at least nine weeks.

Treatments beyond one year were continued for a significant (36.5%) proportion of the patients. This is understandable for the four patients, who completed the planned 18-infusion treatment, but with delays, and for the patient who had disease progression. Most of the longer than one year treatments were related to the use of trastuzumab after surgery (neoadjuvant), the duration of which was added to that of the adjuvant setting. Neoadjuvant use of trastuzumab was off-label at the time of the study and although its benefit has been shown for locally advanced breast cancer, in terms of improvement of 3-year event-free survival (+15%), the total duration of treatment (neoadjuvant followed by adjuvant) in the trial was 52 weeks (13). Hence, trastuzumab has been recently indicated in Europe (November 2011) in combination with neoadjuvant chemotherapy followed by adjuvant monotherapy for a one year duration. Trials have tested longer durations (i.e. 64-76 weeks) and associations of anti-HER2 agents in the neoadjuvant/adjuvant setting but long-term survival results are not yet available (14). Currently, for tolerance and financial reasons, it appears wise to limit the total duration of trastuzumab to one year for patients needing pre-operative chemotherapy.

In conclusion, 12.5% of patients with early HER2-positive breast cancer discontinued adjuvant trastuzumab treatment in our center. The rate of termination due to cardiac problems was low. Our study also revealed a substantial proportion of treatments longer than one year due to pre-operative administrations.

References


Received June 28, 2012
Revised August 29, 2012
Accepted August 31, 2012