Review of utilization of trastuzumab in the adjuvant treatment of breast cancer in four University Teaching Hospitals in Quebec, Canada: a 2 year follow-up of our first year of use.

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BACKGROUND

In 2005, trastuzumab was incorporated into clinical practice for the adjuvant treatment of Her-2 over-expressing breast cancer. The Therapeutic Drug Management Program (TDMP) in collaboration with the Comité d'évolution des pratiques en oncologie (CEPO) wrote in 2005 practice guidelines to promote the optimal use of trastuzumab in adjuvant treatment of breast cancer in Quebec. The preliminary results of compliance to criteria were previously presented at ASCO in 2008[1]. This is a two-year follow-up of outcomes and toxicity.

OBJECTIVES

1. Measure compliance of trastuzumab use to prespecified criteria in adjuvant treatment of breast cancer (results previously reported[1])
2. Describe treatment received by patients
3. Measure efficacy and cardiac toxicity associated with trastuzumab use

METHODS

A review of pharmacy databases was done to identify patients who received trastuzumab between June 1st 2005 and May 31st 2006. Every patient's medical and pharmacy records were reviewed for pathology, adverse events and outcomes. Patients who received trastuzumab for other indications than adjuvant treatment for breast cancer were excluded from this analysis. Data cutoff was June 30th 2008.

RESULTS

Two hundred and eleven patients received at least one dose of trastuzumab between June 1st 2005 and May 31st 2006. Ninety of them received trastuzumab for adjuvant treatment of breast cancer. All patients had proven Her-2 positive tumors by FISH or 3+ IHC. Median age of patients was 56 years. Most of the patients completed surgery before the start of trastuzumab. Sixty percent of the patients had lymph node involvement and 53% received radiation therapy. Forty percent of the patients received hormonal therapy (Table 1). Most of the patients had stage I or II breast cancer (Figure 1).

The majority of the patients (81%) received an anthracycline followed by trastuzumab with or without a taxane. (Figure 2) Trastuzumab was administered according to the "every 3 week" regimen in 93% of the patients (Table 2). These patients received a mean of 16 doses on a median twelve-month period. Only 2 patients received the weekly regimen and 4 patients received a "mixed" regimen of weekly followed by "every 3 weeks".

Twenty patients (22%) had to discontinue treatment before the end of schedule, half of them because of cardiac toxicity, 3 for other unspecified adverse events and 2% because of progression. Five patients (6%) developed brain metastasis while on therapy.

Patients who discontinued treatment received a mean of 9.7 doses over 7 months. (Figure 4)

Three patients temporarily stopped trastuzumab because of a lower LVEF but were able to complete the total course of treatment, after LVEF returned to a normal level. Information for LVEF was missing for 27% of patients at baseline and in 53% of patients after the end of trastuzumab treatment. (Table 3)

After a median follow-up of 751 days (155-1141) with data available for 84 patients, 2 year-progression-free survival (PFS) was estimated at 80% and 2 year-overall survival was estimated at 99%.

Figure 1: Disease stages

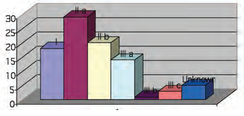


Figure 2: Chemotherapy used

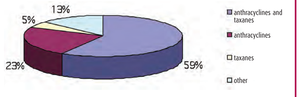


Figure 3: Patients with at least one LVEF value below 50%

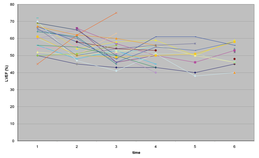


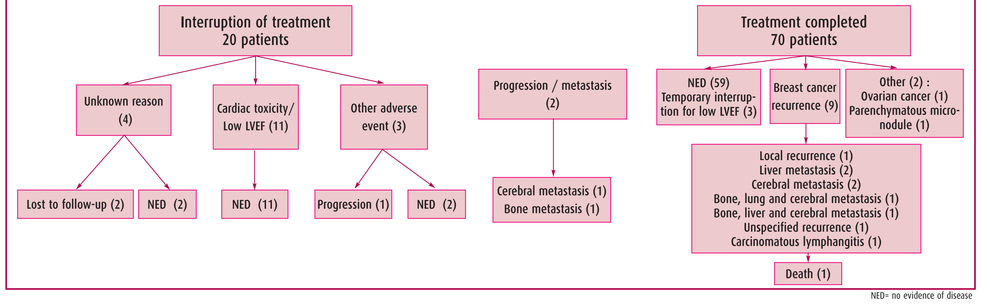
Table 1: Patient characteristics

	n=90	%
Median age (range) years	56 (30-88)	
Surgery completed	86	95
Tumor > 2 cm or ≤ 5 cm	37	41
Involved nodes	54	60
Receiving hormonal therapy	36	40
Radiation therapy	58	53

Table 2: Trastuzumab use

		weekly	mixed (weekly than q3w)	every 3 weeks	discontinued
Number of patients	90	2 (2%)	4 (4%)	84 (93%)	20 (22%)
Mean number of doses	17.3 (2-52)	38.5 (25-52)		16 (2-37)	9.7 (2-17)
Median duration of therapy	12 months (2.5-42)	8.8 months (5.6-12)		12 months (1.5-24)	6.8 months (1.5-12.6)

Figure 3: 90 patients received trastuzumab for adjuvant treatment of breast cancer between June 1st 2005 and May 31st 2006



NED= no evidence of disease

DISCUSSION

The results presented here are a retrospective analysis of the first year of use of trastuzumab in the adjuvant setting, in 4 hospitals. Hence, it has the limitations of a retrospective report with few patients. Regardless, our results are comparable to published data for outcomes. Only one death was reported but our follow-up is relatively short.

Trastuzumab was administered every 3 weeks to minimize impact on clinics and to facilitate treatment for patients. Surprisingly, patients received 16 doses instead of 17, probably because of miscalculations of dates.

We did have more cardiac toxicity then what was previously reported. According to the definition of significant LVEF decrease from the HERA trial (LVEF decrease of more than 10% from baseline or a value < 50%), 12 % of our patients were affected[2]. In comparison, the HERA trial reported that only 7.08% of the patients suffered from a LVEF decrease.

Table 3: LVEF follow-up

Mean LVEF before trastuzumab (n=66)	61.5 % [45 %-81 %]
(patient w/o baseline measure)	27%
Mean number of LVEF measures	3.1 [0-7]
Mean LVEF after trastuzumab	55.6 % [40-73]
Mean number of LVEF measures after trastuzumab	1.4 [1-4]
(pt w/o post-trastuzumab LVEF measure)	53%

Table 4: Cardiac toxicity and interruption of treatment

	n=22
Mean initial LVEF	61.1% [45-72]
No baseline LVEF	5
Number of patients with at least one measure:	
45 < FEV < 50	11
50 < FEV < 55	15
< 45	4
Mean reduction of LVEF between measures	6%
Largest difference between measures	23%
Largest difference between baseline and lowest value	32%
Mean LVEF measure after treatment	47.8 % [40-58]

Also, the mean decrease in LVEF in our study was 6%. The HERA trial reported a decrease of 3%, PACS-04 a reduction of 1.7% and N9831, a decrease of 2.8%. Cardiac toxicity was reported in 24% of our patients but only 12% of our patients stopped trastuzumab for this reason, which is less in comparison of N9831 and NSABP B-31 (15% and 19% respectively)[3-5]. This might be explained by the concomitant use of taxanes with trastuzumab in these studies.

LVEF follow-up seems to be a recurrent problem in our centers. Many LVEF values were missing for analysis. Patients in Quebec may have their tests done in outpatient clinics and their tests results are then sent to the hospital for archives. Most hospitals' medical records are working with a paper version of patient's chart with almost no electronic documentation. Some reports might have been misplaced, explaining some, but not all missing LVEF values. Recommendations were made to the hospitals to improve organization and scheduling of MUGA scans in advance in order to optimize follow-up.

Five patients were reported to have brain metastasis, including one during trastuzumab therapy. Trastuzumab does not cross the blood-brain barrier and it has been reported that patients on trastuzumab might develop brain metastasis.

Although trastuzumab is not known for causing many adverse events, information concerning other type of adverse events was not systematically collected. It would have been interesting to report that data as well.

CONCLUSION

Utilization of trastuzumab in Quebec is adequate. Patients received optimal doses and regimens. Cardiac toxicity was superior in our study. Cardiac evaluation should be performed and documented systematically at baseline, every 3 months and at the end of trastuzumab therapy.
Our follow-up needs better documentation. Patients need to be evaluated at baseline, and at the end of treatment.

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