Review of Utilization of Trastuzumab in the Adjuvant Treatment of Breast Cancer in Four University Teaching Hospitals in Québec, Canada

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BACKGROUND

The use of trastuzumab in the early treatment of breast cancer is now a standard of care since the presentation at ASCO 2005 of the results of two major clinical trials. Trastuzumab has been widely incorporated into clinical practice guidelines. The Therapeutic Drug Management Program (TDMP – www.pgtm.qc.ca) in collaboration with the Comité d'évolution des pratiques en oncologie du Québec (CEPO), wrote practice guidelines to promote the optimal use of trastuzumab in adjuvant treatment of breast cancer in Québec, Canada. The present study illustrates the first year of utilization of trastuzumab in the adjuvant setting. The government of Québec announced in summer of 2005 that trastuzumab would be funded for adjuvant treatment.

OBJECTIVES

- To perform a descriptive analysis of the general use of trastuzumab in our centers.
- To measure the conformity of trastuzumab utilization in the adjuvant setting based on predefined criteria:

Predefined Criteria

adjuvant treatment concomitant to or following chemotherapy
completely resected tumor
tumor overexpressing Her-2 protein (FISH + or IHC 3+)
tumor ≥ 1 cm or < 1 cm with positive lymph nodes
LVEF > 55% measured before start of therapy

- To evaluate cardiotoxicity and regular follow-up for patients receiving trastuzumab in the adjuvant setting.

METHODS

A review of pharmacy databases was performed to identify patients receiving trastuzumab between June 1st 2005 and May 31st 2006. Every patient file including trastuzumab was reviewed. Patients' medical records were also reviewed for pathology and side effects.

RESULTS

A) All patients

211 patients received trastuzumab in that time period with 108 (51%) patients receiving it in the metastatic, 91 (44%) in the adjuvant and 11 (5%) in the neoadjuvant settings.

Table 1

Patient characteristics	N = 211
Mean Age	
• All patients	57 y
• Adjuvant and neoadjuvant treatment	55 y
• Metastatic disease	59 y
Positive hormone receptors (ER and/or PR)	N (%)
• Adjuvant treatment	46 (51%)
• Neoadjuvant treatment	5 (45%)
• Metastatic disease	57 (54%)

Table 2

Indication for Trastuzumab use	N = 211 (%)
Adjuvant therapy	91 (44%)
Neo-adjuvant therapy	11 (5%)
Metastatic disease	108 (51%)
Other indication	1 (0.5%)

Her-2 test used by centers

It was possible to validate a positive test by FISH or by IHC 3+ in 96% of the patients (figure 1). The data was missing in the files for the other 4%. For patients treated in the adjuvant setting, all IHC-2+ tests were confirmed by a FISH test, which also confirmed 27% of the IHC-3+ test. Data concerning the metastatic patients was often incomplete (25%) and could not be corroborated in the patient files.

B) Patients receiving trastuzumab in the adjuvant setting

In the adjuvant setting, the mean age of the patients was 55 and 51% were hormone receptor positive. The pathology reports cited that 95% of patients had their tumor completely removed and 60% had node involvement. Disease stages are shown in figure 2.

The mean delay between surgery and first dose of trastuzumab was 204 days. Most of the patients received the "q 3 week" regimen (92%) (figure 3). At the end of our data collection, the average number of doses received by patients was 9. Only one patient had finished the complete treatment at the end of our study. 87% of patients were still receiving treatment at the end of May 2006.
The average delay between the last dose of chemotherapy and the first dose of trastuzumab was 91 days. Also, most patients received an anthracycline or a taxane containing regimen, prior to (55%) or concomitant (37%) with trastuzumab. Figure 4 details the various types of chemotherapy administered to patients in our centers. Although 51% of patients had positive hormonal receptors, only 36% received adjuvant hormonal therapy after their chemotherapy.

Monitoring for cardiotoxicity was mandatory for all patients. The guidelines suggested a baseline evaluation (pre-trastuzumab) and a reevaluation every 3 months. **Three (3,3%) patients had to stop treatment because of cardiotoxicity, 2 (2%) for other non specified side effects one (1%) for progression and 3 (3.3%) for other undisclosed reasons.**

Table 3

Reason of non-conformity	N = 91
Incomplete resection of tumor	4
Node negative AND tumor < 1 cm	4
Pathology report missing from file or incomplete and LVEF pre-trastuzumab not available	1
HER-2 test not available AND incomplete pathology report	1
HER-2 test not available	2
HER-2 test not available AND LVEF pre-trastuzumab not available	1

Table 4

Results of conformity	N = 91
% of patients meeting all criteria	54 (59%)
% of patients meeting all criteria but with a LVEF ≥ 50 % and < 55%	13 (14%)
% of patients meeting all criteria but with unavailable pre-trastuzumab LVEF or with other missing data	11 (12%) 5 (5%)
% of patients not meeting criteria	8 (9%)

Table 5

Monitoring of cardiotoxicity		N = 91
Mean Initial LVEF	62.3%	[50,82]
Patients with undocumented baseline LVEF		15 (17%)
During treatment		
Patients with at least one value :		
	< 45%	1
	45% ≤ LVEF < 50%	3
	50% ≤ LVEF < 55%	12
Mean reduction of LVEF between 2 measures		6.1%
Greater variation between measures		28%
Greater variation between baseline and 1st measure		28%
Mean time between measures [min,max]	89.5 days	[22,320]
Patients with more than 90 days between 2 measures		19
Types of exam performed for LVEF evaluation		
	Doppler	23 (25%)
	MUGA scan	53 (58%)
	unknown	15 (17%)

DISCUSSION

The overall conformity analysis showed that only 59% of the patients receiving trastuzumab met all criteria. When the patients with a baseline LVEF > 50% but < 55%, were considered eligible, the conformity rose to 83%. Missing data prevented conformity evaluation for 13% of the cases. Only 4 cases did not meet the criteria of tumor < 1 cm with node involvement, and 4 cases had not a completely removed tumor (positive margins) (figure 5). Physicians in our centers explained that adjuvant trastuzumab therapy was given in some high-risk patients.
Although cardiotoxicity was seen in 3% of our patients, which is less than reported in the HERA trial and in the NSABP B-31 and NCCTG N9831 trial, our patients had received only an average of 9 doses. Long-term follow-up and baseline values are mandatory, and measures have been taken in our centers to ensure regular monitoring. In many cases, missing data prevented conformity, which could be remediated through improved documentation of patient files.

CONCLUSION

Overall, the review shows a good conformity to practice guidelines. Only 9% of reviewed cases clearly did not conform to the predetermined criteria. Recommendations to improve documentation of LVEF and side effects in patient files were made to clinicians and tools were developed to facilitate follow-up of patients in the different centers.

Figure 1: **Her-2 test used by centers**

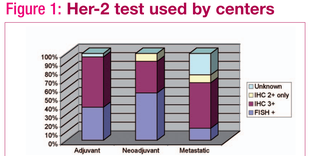

Figure 2: **Disease stage**

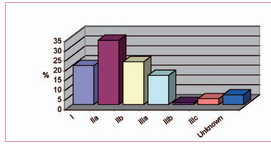

Figure 3: **Administration Schedule**

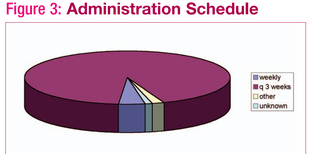

Figure 4: **Adjuvant chemotherapy used**

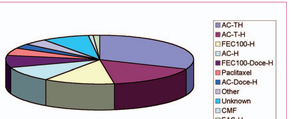

Figure 5: **Conformity to criteria**