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Editorial

EDITORIAL

Trastuzumab: Weighing the Benefits and the Risks

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Within this issue of the Journal, Rushton and colleagues (1) report the outcomes of premature discontinuation of trastuzumab on breast cancer outcomes in 5547 women with early-stage HER2-positive breast cancer treated with the adjuvant trastuzumab. Using administrative claims data in Ontario, Canada, for women treated for HER2-positive breast cancer 2007-2016, they assessed the impact of full trastuzumab treatment (17-18 cycles) on cancer outcomes as compared with early discontinuation ([1] discontinuation for cardiac events [CEs], [2] no CEs but <16 cycles of trastuzumab, and [3] no CEs, <16 cycles of trastuzumab but >30 days since last trastuzumab) (2). The 5-year disease-free survival (DFS) was statistically significantly lower for those women who did not receive full treatment regardless of the cause of premature discontinuation (94.1% vs 80%, 81.4%, 82.4%). Overall survival (OS) was also inferior in those with premature discontinuation of trastuzumab regardless of cause (95.0% vs 84.4%, 82.8%, 83.7%). It appears from this analysis that using trastuzumab for durations less than 17-18 cycles results in inferior cancer outcomes.

Although the use of trastuzumab in the (neo)adjuvant setting for HER2-positive breast cancer improves both OS and DFS, several different clinical trials have been conducted in an effort to investigate the optimal duration of this treatment. Initially, 12 months of trastuzumab was chosen rather arbitrarily. In the adjuvant setting, chemotherapy with trastuzumab was demonstrated to improve OS in the combined analysis of the North Central Cancer Treatment Group N9831 and the National Adjuvant Breast and Bowel Project B-31 clinical trials (3). OS improved by 40%, with DFS improving by 37% at a median follow-up of 8.4 years. Based on these studies, 1 month of trastuzumab (17-18 cycles) became the standard of care. In the HERA study of more than 5000 women, there was no improvement in DFS with 2 years of trastuzumab (69% in both the 1- and 2-year arms) or OS (79% and 80%) (4). The incidence of cardiac toxicity was lower in those treated with 1 year of trastuzumab.

More recent studies have evaluated whether an even shorter duration of trastuzumab can have the same outcomes (Table 1). In the PHARE study of 3380 women randomized to 6 vs 12 months of trastuzumab, noninferiority of 6 vs 12 months based on prespecified criteria could not be claimed (hazard ratio = 1.08, 95% confidence interval = 0.93 to 1.25). There were more CEs in the 12-month group, however (5.7% vs 1.9%, $P < .0001$) (5). The Hellenic Oncology Research Group also assessed the impact of 6 vs 12 months of trastuzumab in 481 patients with early-stage HER2-positive breast cancer. The 3-year DFS was 95.7% and 93.3% in favor of the 12-month treatment group (hazard ratio = 1.57, $P = .137$). There was no difference in OS and cardiac toxicity (6). Three other more recent studies demonstrate conflicting results. SHORT-HER (Multicentric randomized phase 3 trial of 2 different adjuvant chemo regimens plus 3 vs 12 months of trastuzumab in HER2+ breast cancer patients) and Synergism or Long Duration (SOLD) evaluated the use of 9 weeks compared with 12 months of trastuzumab in combination with chemotherapy (differing chemotherapy regimens for SHORT-HER, same for SOLD). Noninferiority could not be achieved. In SHORT-HER, the 5-year DFS was 85% in the 9-week arm and 88% in the 12-month arm, not achieving prespecified criteria (7,8). In the PERESPHONE trial of 2045 early-stage HER2-positive breast cancer patients, 4-year DFS was 89.4% in the 6-month arm compared with 89.8% in the 12-month arm ($P = .011$). Cardiac events were higher in the 12-month arm of trastuzumab (3% vs 8%, $P < .0001$) (9). Based on these results, shortened trastuzumab courses may be an option for those at high risk for cardiac dysfunction.

With the current studies available, 12 months of adjuvant trastuzumab should be continued as the standard of care for women with HER2-positive breast cancer receiving chemotherapy plus trastuzumab alone. Currently, more and more patients with HER2-positive breast cancer are being treated in the neoadjuvant setting, and with dual HER2-blocking agents (blocking both HER2 and HER3) using trastuzumab plus pertuzumab though. In the United States, for patients with tumors greater than 2 cm, dual HER2 blockade has become the standard of care based on the results for the NEOSPHERE and TRYPHAENA trials (10,11). Following neoadjuvant chemotherapy for HER2-positive tumors, individuals may receive trastuzumab alone, trastuzumab plus pertuzumab as in the APHINITY trial (12), or adjuvant trastuzumab emtansine for 14 cycles as per the KATHERINE study (13). It is clear from the KATHERINE study that adjuvant trastuzumab emtansine is superior to trastuzumab alone for those with residual disease from neoadjuvant chemotherapy. It is suggestive that doublet therapy (trastuzumab plus pertuzumab) is superior to trastuzumab alone in the adjuvant setting. It is unclear, however, how premature discontinuation of trastuzumab affects outcomes in individuals who received

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Table 1. Prospective trials evaluating adjuvant trastuzumab duration and associated breast cancer outcomes*

Trial	Reference	No.	Treatment arms	DFS	OS	Cardiac events
HERA	Cameron et al., 2017 (4)	5102	Obs vs T 1y vs T 2y	63% vs 69% vs 69% (at 10 y)	73% vs 79% vs 80%	0% vs 4.4% vs 7.3%
NSABP B31/NCCTG 9831	Perez et al., 2014 (3)	3177	Obs vs T 1 y	62.2% vs 73.7% (at 10 y)	75.2% vs 84.0%	3 vs 9 CV deaths
SOLD	Joensuu et al., 2018 (8)	2100	9 wk vs 1 y T	88% vs 90.5% (at 5 y)	Not reported	21 vs 36 cases
PHARE	Pivot et al, 2019 (5)	3384	0.5 vs 1 y T	78% vs 80% (at 7.5 y)	81% vs 82%	Equivalent
HORG	Mavroudis et al., 2015 (6)	481	0.5 vs 1 y T	93% vs 96% (at 3 y)	Equivalent	Equivalent
PERSEPHONE	Earl et al., 2018 (9)	2045	0.6 vs 1 y T	89.4% vs 89.8% (at 4 y)	Not reported yet	3% vs 8%
SHORT-HER	Conte et al., 2018 (7)	1254	9 wk vs 1 y T	85% vs 88% (at 5 y)	95.0% vs 95.2%	4.3% vs 13.1%

*CV= cardiovascular events; DFS = disease-free survival; OS = overall survival; T = trastuzumab.

neoadjuvant trastuzumab plus pertuzumab or how premature discontinuation of trastuzumab affects those who achieved a complete pathologic response after neoadjuvant chemotherapy in which they may do extremely well regardless. For example, in triple-negative breast cancer, additional therapy following a complete pathologic response does not improve outcomes (14). It is also not clear how HER2 heterogeneity plays into these results (15). Stratifying by molecular subtypes of HER2-positive tumors or estrogen status may help outline who benefits from trastuzumab or a drug conjugate. Other studies, particularly for low-risk HER2-positive breast cancers, suggest that overall patients do extremely well with little HER2-based therapies (16).

Today, it seems clear that 12 months of trastuzumab remains the standard of care. Further efforts should be made to risk-stratify patients, on genomic profile, HER2 heterogeneity, and response to neoadjuvant chemotherapy, determining who is at highest risk of recurrence, because these individuals may benefit from dual HER2 blockade or consideration of trastuzumab emtansine in the adjuvant setting. These individuals also should not have a shortened course of trastuzumab. Similar risk stratification from a cardiac perspective should be performed in all patients. Six months of trastuzumab may be reasonable to consider for those at high risk for cardiac dysfunction and a low biologic risk of recurrence. Finally, shorter courses of trastuzumab may be reasonable to consider, particularly in low- to middle-income countries where the resources are more limited.

Notes

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