Real-World Outcomes of Adjuvant Chemotherapy for Node-Negative and Node-Positive HER2-Positive Breast Cancer

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ABSTRACT

Background: Comparative real-world outcomes for patients with HER2-positive (HER2+) breast cancer receiving adjuvant trastuzumab outside of clinical trials are lacking. This study sought to retrospectively characterize outcomes for patients with node-negative and node-positive breast cancer receiving adjuvant trastuzumab in combination with docetaxel/cyclophosphamide (DCH), docetaxel/carboplatin/trastuzumab (TCH), or fluorouracil/epirubicin/cyclophosphamide followed by docetaxel/trastuzumab (FEC-DH) chemotherapy in Alberta, Canada, from 2007 through 2014. **Methods:** Disease-free survival and overall survival (OS) analyses for node-negative cohorts receiving DCH (n=111) or TCH (n=371) and node-positive cohorts receiving FEC-DH (n=146) or TCH (n=315) were compared using chi-square, Kaplan-Meier, or Cox multivariable analysis where appropriate. **Results:** Median follow-up was similar in node-negative (63.9 months) and node-positive (69.0 months) cohorts. The 5-year OS rates in patients with node-negative disease receiving DCH or TCH were similar (95.2% vs 96.9%; *P*=.268), whereas 5-year OS rates were higher but nonsignificant for patients with node-positive disease treated with FEC-DH compared with TCH (95.2% vs 91.4%; *P*=.160). Subgroup analysis of node-positive cohorts showed significantly improved OS with FEC-DH versus TCH in patients with estrogen receptor (ER)/progesterone receptor (PR)–positive breast cancer (98.3% vs 91.6%, respectively; *P*=.014). Conversely, patients with ER/PR-negative disease showed a nonsignificant trend toward higher OS rates with TCH versus FEC-DH (91.6% vs 83.3%, respectively; *P*=.298). Given the retrospective design, we were unable to capture all potential covariates that may have impacted treatment assignment and/or outcomes. Furthermore, cardiac toxicity data were unavailable. **Conclusions:** Survival rates of patients with HER2+ breast cancer in our study are comparable to those seen in clinical trials. Our findings support chemotherapy de-escalation in patients with node-negative disease and validate the efficacy of FEC-DH in those with node-positive disease.

J Natl Compr Canc Netw 2019;17(1):47–56
doi: 10.6004/jnccn.2018.7066

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Amplification or overexpression of the *HER2* gene comprises 15% to 25% of early-stage breast cancers.[1,2] Associated with an aggressive phenotype, survival for HER2-positive (HER2+) breast cancer has significantly improved with the use of HER2-targeted therapies, such as trastuzumab.[3–5] However, outcomes for patients with HER2+ breast cancer treated outside of clinical trials are limited.[6,7]

In small, node-negative, HER2+ tumors, the benefit of adding trastuzumab to adjuvant chemotherapy is well described.[8–11] However, the potential for overtreatment and toxicity associated with use of third-generation chemotherapy regimens is of concern. After the E1199 clinical trial[12] established the equivalence of docetaxel every 3 weeks and weekly paclitaxel, 2 single-arm phase II trials evaluated the utility of short-course docetaxel/cyclophosphamide (DCH for 4 cycles)[13] or paclitaxel (weekly for 12 weeks)[14] in combination with trastuzumab for low-risk HER2+ breast cancer. Both trials demonstrated high disease-free survival (DFS) and/or recurrence-free survival rates (>97%).

In node-positive HER2+ disease, the benefits of adjuvant trastuzumab in combination with chemotherapy have been shown in the BCIRG-006[5] and NSABP B-31/NCCTG N9831[4] clinical trials. Treatment with chemotherapy plus trastuzumab was superior to chemotherapy alone. In the final update of BCIRG-006, AC-TH (doxorubicin/cyclophosphamide followed by docetaxel/trastuzumab) was associated with nonsignificantly higher overall survival (OS) compared with TCH (docetaxel/carboplatin/trastuzumab) at the detriment of more chemotherapy and higher rates of cardiac and leukemic events.[15] Despite an abundance of data comparing AC followed by taxane/trastuzumab to TCH, a paucity of data exists comparing FEC-DH (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel/trastuzumab) versus either TCH or AC followed by taxane/trastuzumab in the adjuvant setting despite inclusion in ASCO guidelines.[16]

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We retrospectively evaluated survival outcomes for 2 groups of patients with HER2+ disease: those with (1) node-negative disease receiving either DCH or TCH, and (2) node-positive disease receiving either FEC-DH or TCH in the adjuvant setting.

Methods

Patient Selection

All women diagnosed from 2007 through 2014 with stage I–III, HER2+ breast cancer who received DCH for 4 cycles, TCH for 6 cycles, or FEC-DH for 6 cycles followed by up to 1 year of trastuzumab in the province of Alberta, Canada, were identified using the Alberta Cancer Registry (ACR). Patients were stratified into 2 cohorts: those with (1) node-negative disease who received DCH or TCH or (2) node-positive disease who received FEC-DH or TCH (Figure 1).

Patient and pathology characteristics (Tables 1 and 2, for node-negative and node-positive cohorts, respectively), treatment characteristics (Tables 3 and 4, for node-negative and node-positive cohorts, respectively), and recurrence information (date and sites: local, bone, visceral, brain) were collected from the ACR and, when required, manual chart review. Patient characteristics included age, menopausal status, and comorbidity data using the updated Charlson comorbidity index (U-CCI).[17] Pathology characteristics included AJCC tumor size, tumor grade, lymphovascular invasion (LVI), and histologic type. Treatment characteristics included chemotherapy regimen and cycles completed, surgery type, radiotherapy prescription, and adjuvant hormone therapy prescription. This study was approved by the Health Research Ethics Board of Alberta.

Statistics

Patient characteristics were compared using chi-square test, Fisher exact test, *t*-test, or Mann-Whitney U test where appropriate. For survival calculations, time from breast surgery to last follow-up or event was used. DFS, OS, and breast cancer–specific survival (BCSS) were compared using the Kaplan-Meier method (with log-rank analyses). A Cox proportional hazards model was used for survival estimates in multivariable analysis of treatment and patient characteristics. Hazard ratios (HRs) and 95% CIs are reported. For all tests, $P<.05$ was considered significant. Statistics were performed using SigmaPlot V13 (Systat Software, Inc) or SPSS Statistics, version 19 (IBM Corporation).

Results

Patients

A total of 1,006 patients with HER2+ breast cancer receiving 1 of 3 treatment regimens (DCH, TCH, or FEC-DH) were identified over a 7-year period. Overall, 19 patients with node-positive disease received

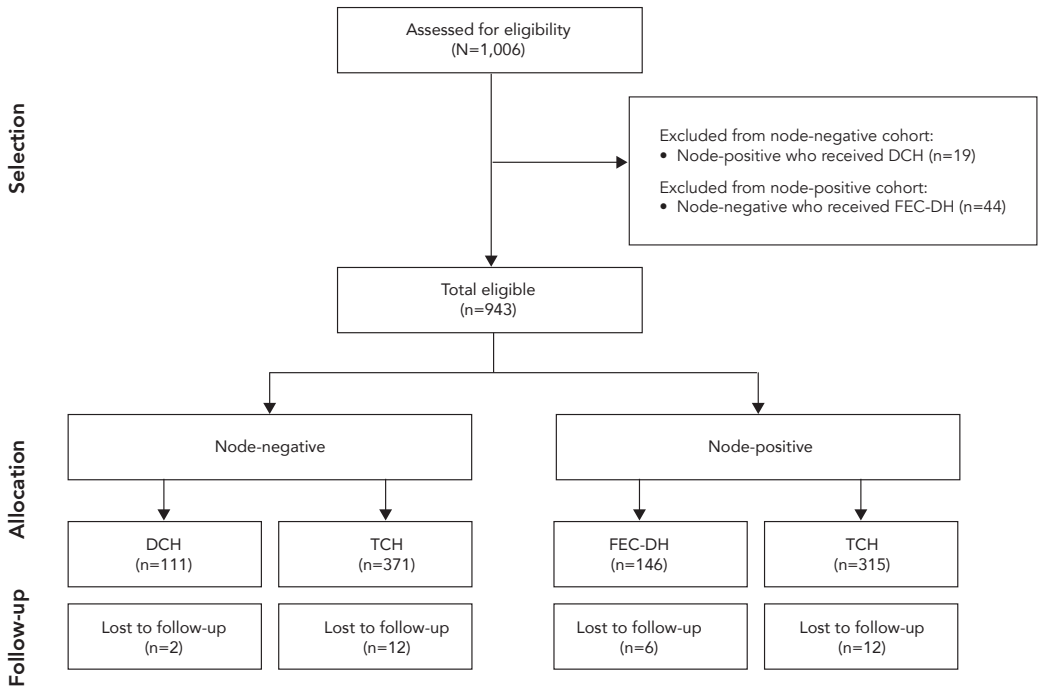

Figure 1. Selection and allocation of node-negative and node-positive cohorts.
Abbreviations: DCH, docetaxel/cyclophosphamide; FEC-DH, fluorouracil/epirubicin/cyclophosphamide followed by docetaxel/trastuzumab; TCH, docetaxel/carboplatin/trastuzumab.

DCH and were thus excluded from the node-negative cohort. Conversely, 44 patients with node-negative disease received FEC-DH and were excluded from the node-positive cohort. A total of 943 patients were eligible for allocation to the node-negative (DCH or TCH) and node-positive (FEC-DH or TCH) cohorts (Figure 1).

Node-Negative Cohort

Characteristics

In the node-negative cohort, 482 patients (DCH, n=111; TCH, n=371) were included for analysis (Table 1). Clinicopathologic features were not significantly different between DCH and TCH cohorts. Patients receiving DCH were slightly

Table 1. Patient Characteristics for Node-Negative Cohort

	DCH (N=111)		TCH (N=371)		
	n	%	n	%	*P* Value
Median age (range), y	56	(34–74)	53	(28–76)	<.001[a]
Menopausal status					.467
Premenopausal	45	40.5	164	44.2	
Postmenopausal	66	59.5	207	55.8	
U-CCI					.053
0	89	80.2	317	85.4	
1	17	15.3	50	13.5	
≥2	5	4.5	4	1.1	
Histology					.126
IDC	94	84.7	330	88.9	
ILC	6	5.4	7	1.9	
Other	11	9.9	34	9.2	
T stage					.028*
T1	77	69.4	207	55.8	
T2	34	30.6	160	43.1	
T3	0	0	4	1.1	
Unknown	0	0	0	0	
N stage					NA
N0	111	100	371	100	
AJCC stage					.024[a]
I	77	69.4	204	55.0	
II	34	30.6	166	44.7	
III	0	0	1	0.3	
Tumor grade					.258
1	2	1.8	5	1.3	
2	35	31.5	89	24.0	
3	74	66.7	276	74.4	
Unknown	0	0	1	0.3	
LVI					.102
Present	25	22.5	113	30.5	
Absent	84	75.7	251	67.7	
Unknown	2	1.8	7	1.9	
Hormone receptor status					.289
ER+/PR+	90	81.1	283	76.3	
ER–/PR–	21	18.9	88	23.7	

Abbreviations: DCH, docetaxel/cyclophosphamide; ER, estrogen receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; NA, not applicable; PR, progesterone receptor; TCH, docetaxel/carboplatin/trastuzumab; U-CCI, updated Charlson comorbidity index.
[a]*P*<.05.

Table 2. Patient Characteristics for Node-Positive Cohort

	FEC-DH (N=146)		TCH (N=315)		
	n	%	n	%	*P* Value
Median age (range), y	50	(25–74)	54	(24–81)	.002[a]
Menopausal status					.003[a]
Premenopausal	85	58.2	137	43.5	
Postmenopausal	61	41.8	178	56.5	
U-CCI					.451
0	120	82.2	273	86.7	
1	23	15.8	37	11.7	
≥2	3	2.1	5	1.6	
Histology					.036[a]
IDC	123	84.2	288	91.4	
ILC	4	2.7	2	0.6	
Other	19	13.0	25	7.9	
T stage					.002[a]
T1	34	23.3	110	34.9	
T2	87	59.6	180	57.1	
T3	24	16.4	24	7.6	
Unknown	1	0.7	1	0.3	
N stage					.324
N1	81	55.5	195	61.9	
N2	43	29.5	73	23.2	
N3	22	15.1	47	14.9	
AJCC stage					.03[a]
I	0	0	0	0	
II	71	48.6	187	59.4	
III	75	51.4	128	40.6	
Tumor grade					.280
1	0	0	5	1.6	
2	31	21.2	60	19.2	
3	115	78.8	248	79.2	
Unknown	0		2		
LVI					.097
Present	109	74.7	211	67.0	
Absent	35	24.0	99	31.4	
Unknown	2	1.3	5	1.6	
Hormone receptor status					.407
ER+/PR+	115	78.8	237	75.2	
ER–/PR–	31	21.2	78	24.8	

Abbreviations: ER, estrogen receptor; FEC-DH, fluorouracil/epirubicin/cyclophosphamide followed by docetaxel/trastuzumab; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; PR, progesterone receptor; TCH, docetaxel/carboplatin/trastuzumab; U-CCI, updated Charlson comorbidity index.
[a]*P*<.05.

older (median age, 56 years; range, 34–74 years) compared with those receiving TCH (median age, 53 years; range, 28–76 years; *P*<.001). A trend toward lower (U-CCI, 0) patient comorbidities was seen with TCH (85.4%) relative to DCH (80.2%; *P*=.053), and there was an imbalance in the distribution of T1 (more frequently treated with DCH) and T2 tumors (more frequently treated with TCH; *P*=.028); few T3 tumors were seen in either the DCH or TCH groups. No significant differences were seen in sequential treatment modalities or completion of chemotherapy (Table 3).

Patterns of relapse are shown in Figure 2. No bone only or brain relapses were seen in the DCH cohort. In the node-negative TCH cohort, brain (evaluated separately) was involved in 32% of relapses. Relapse characteristics for both cohorts are listed in supplemental eAppendix 1, available with this article at JNCCN.org.

Outcomes

Median follow-up for the node-negative cohort was 63.9 months. Five-year survival rates remained high for both the DCH and TCH cohorts, with no significant differences seen in DFS (92.3% vs 95.2%; *P*=.485), OS (95.2% vs 96.9%; *P*=.268), or BCSS (97.1% vs 98.3%; *P*=.285) (Figure 3). In multivariable analysis for OS (Table 5), characteristics with HR <0.67 or >1.5 and nonsignificant trends toward worse outcomes were seen for DCH relative to TCH (HR, 1.956; *P*=.196), T2 relative to T1 tumors (HR, 1.887; *P*=.192), premenopausal relative to postmenopausal status (HR, 0.392; *P*=.105), and hormone receptor–negative relative to hormone receptor–positive tumors (HR, 2.100; *P*=.137). Receipt of radiotherapy, tumor grade, and LVI were not shown to affect survival. Higher number of comorbidities (≥1) significantly affected DFS (HR, 2.83; *P*=.014) but did not affect OS (*P*=.932) or BCSS (*P*=.415) in multivariate analysis.

Node-Positive Cohort

Characteristics

In the node-positive cohort, 461 patients (FEC-DH, n=146; TCH, n=315) were included for analysis (Table 2). Patients receiving FEC-DH were younger (median age, 50 years; range, 25–74 years) than those receiving TCH (median age, 54 years; range, 24–81 years; *P*=.002). Significantly more patients in the FEC-DH cohort were premenopausal (58.2%) than those receiving TCH (43.5%; *P*=.003). No differences were seen in number of comorbidities (*P*=.451).

Comparison of clinical pathologic features between cohorts showed that significantly more patients with larger tumors (>2 cm) were treated with FEC-DH (76.6%) relative to TCH (69.4%; *P*=.002). Consequently, more AJCC stage III tumors (*P*=.03) were treated with FEC-DH (51.4%) relative to TCH (40.6%). Fewer patients treated with FEC-DH had invasive ductal histology (84.2%) relative to TCH (91.4%; *P*=.036). No significant differences were seen in tumor grade, hormone receptor status, or LVI. Cohorts were balanced for those receiving sequential treatment modalities (Table 4). No significant differences were seen in the number of patients completing chemotherapy (*P*=.754).

Relapse patterns were similar except for the frequency of local recurrences (FEC-DH, 38% vs TCH, 13%) as well as combined bone and visceral metastasis (FEC-DH, 23% vs TCH, 41%) (Figure 2). Relapse characteristics for both cohorts are listed in supplemental eAppendix 2.

Outcomes

Median follow-up for the node-positive cohort was 69.0 months, and 5-year survival (Figure 4) exceeded 88% for both cohorts, with a nonsignificant trend favoring FEC-DH over TCH for DFS (92.4% vs 88.5%; *P*=.280), OS (95.2% vs 91.4%; *P*=.160), and BCSS (95.9% vs 92.4%; *P*=.161).

In multivariable analysis (Table 5) for OS, characteristics with HR <0.67 or >1.5 and nonsignificant trends toward worse outcomes were seen for TCH relative to FEC-DH (HR, 1.90; *P*=.117), premenopausal relative to postmenopausal status (HR, 0.608; *P*=.154),

Table 3. Treatment Characteristics for Node-Negative Cohorts

	DCH (N=111)		TCH (N=371)		
	n		n	%	*P* Value
Chemotherapy complete					.060
No (DCH <4; TCH <6)	10	9.0	14	3.8	
Yes (DCH=4; TCH=6)	101	91.0	357	96.2	
Radiotherapy delivered					.850
Yes	55	49.5	180	48.5	
No	56	50.5	191	51.5	
Surgery					.899
Breast-conserving	54	48.6	183	49.3	
Mastectomy	57	51.4	188	50.7	
Hormone therapy					.246
Yes	88	79.3	274	73.9	
No	23	20.7	97	26.1	

Abbreviations: DCH, docetaxel/cyclophosphamide; TCH, docetaxel/carboplatin/trastuzumab.

Table 4. Treatment Characteristics for Node-Positive Cohorts

	FEC-DH (N=146)		TCH (N=315)		
	n	%	n	%	*P* Value
Chemotherapy complete					.754
No (FEC-DH <6; TCH <6)	6	4.1	15	4.8	
Yes (FEC-DH=6; TCH=6)	140	95.9	300	95.2	
Radiotherapy delivered					.265
Yes	129	88.4	266	84.4	
No	17	11.6	49	15.6	
Surgery					.247
Breast-conserving	37	25.3	97	30.8	
Mastectomy	108	74.0	218	69.2	
Unknown	1	0.7	0	0	
Hormone therapy					.470
Yes	109	74.7	225	71.4	
No	37	25.3	90	28.6	

Abbreviations: FEC-DH, fluorouracil/epirubicin/cyclophosphamide followed by docetaxel/trastuzumab; TCH, docetaxel/carboplatin/trastuzumab.

grade 3 relative to grade 2 tumors (HR, 1.780; *P*=.284), presence relative to absence of LVI (HR, 1.568; *P*=.309), and T3 (HR, 2.107; *P*=.231) or T2 (HR, 1.925; *P*=.163) relative to T1 tumors.

With respect to OS for nodal status, N3 (HR, 1.948) did not reach statistical significance relative to N1 (*P*=.148), but N2 did (HR, 2.314; *P*=.032). In analysis for DFS, HRs remained significant for N3 disease (HR, 3.639; *P*=.001) and N2 (HR, 3.037; *P*=.002) relative to N1 (supplemental eAppendix 3). This trend continued for BCSS, with N3 (HR, 2.958; *P*=.031) and N2 disease (HR, 3.467; *P*=.004) showing worse outcomes relative to N1. Lack of radiotherapy adversely affected DFS (HR, 3.510; *P*=.013) but did not affect OS or BCSS.

Subgroup Analysis

In subgroup analysis of patients with node-positive hormone receptor–positive tumors (TCH, n=238; FEC-DH, n=115), OS was superior (*P*=.014) for those treated with FEC-DH (98.3%) compared with TCH (91.6%; *P*=.018) (supplemental eAppendix 4A). DFS was of borderline significance (*P*=.056), even with balanced nodal status between cohorts. Conversely, subgroup analysis of patients with node-positive hormone receptor–nega-

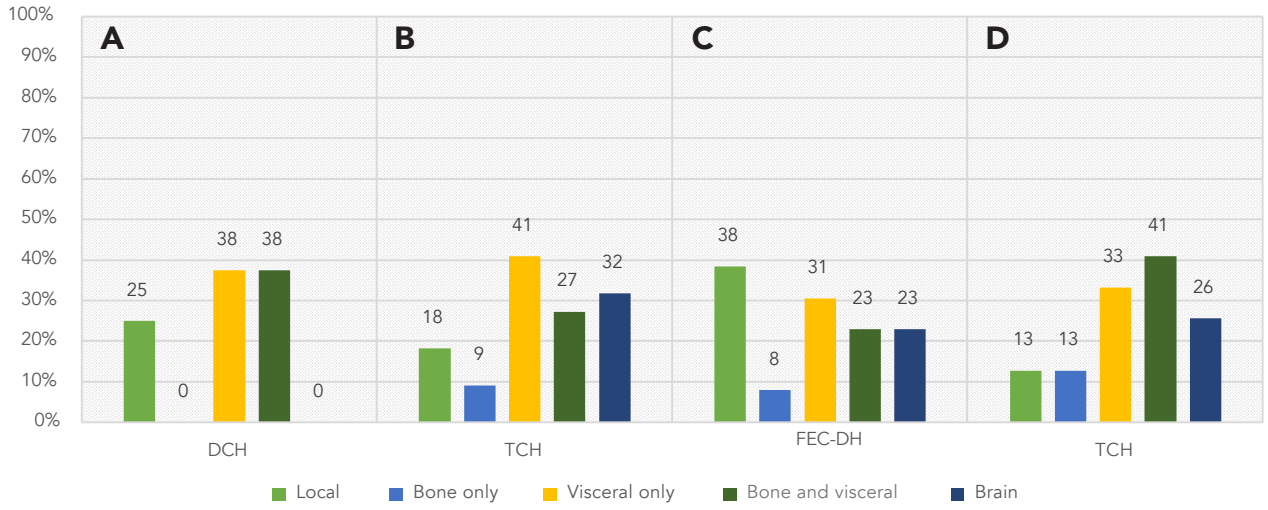

Figure 2. Frequency of recurrence by location and (A, B) node-negative and (C, D) node-positive cohorts for each treatment regimen. Abbreviations: DCH, docetaxel/cyclophosphamide; FEC-DH, fluorouracil/epirubicin/cyclophosphamide followed by docetaxel/trastuzumab; TCH, docetaxel/carboplatin/trastuzumab.

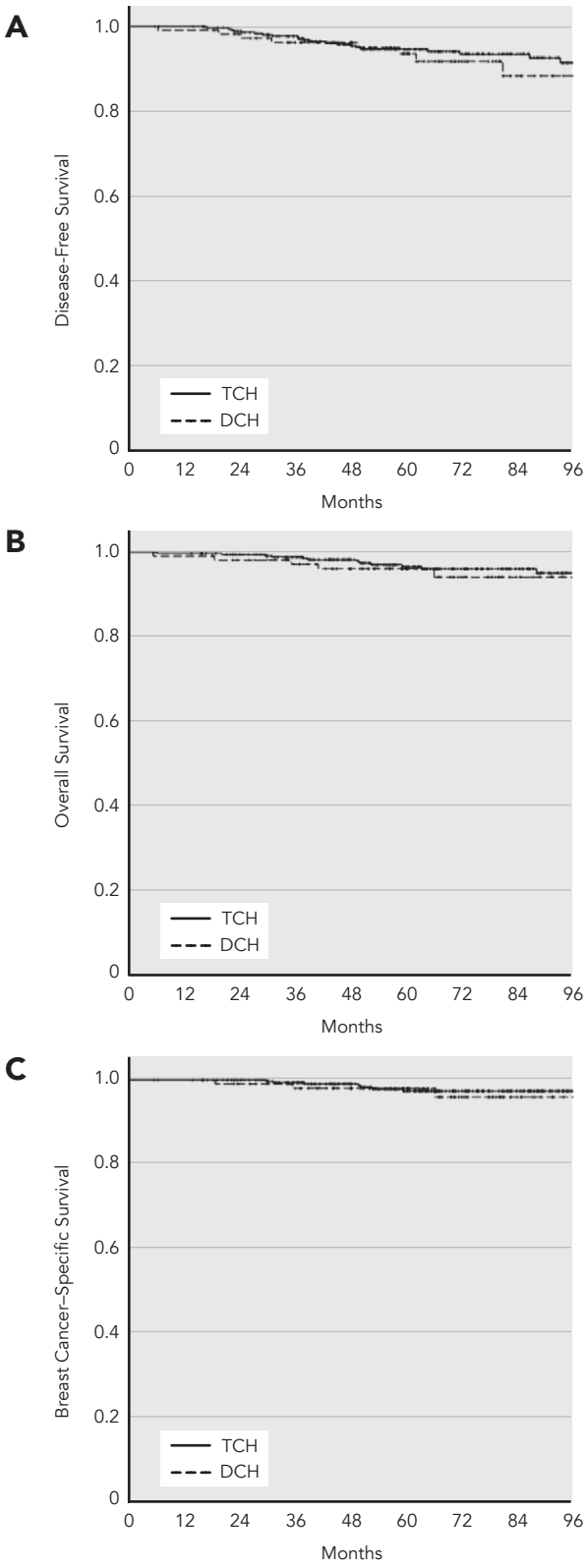

Figure 3. Kaplan-Meier plots for (A) disease-free survival, (B) overall survival, and (C) breast cancer–specific survival for the node-negative cohort.
Abbreviations: DCH, docetaxel/cyclophosphamide; TCH, docetaxel/carboplatin/trastuzumab.

tive tumors showed higher DFS and OS rates for those treated with TCH (n=76; 88.2% and 90.8%, respectively) relative to those treated with FEC-DH (n=30; 83.3% and 83.3%, respectively) (*P*=.272 and *P*=.269, respectively), although this was nonsignificant (supplemental eAppendix 4B).

Discussion

This study addresses several areas in which data are limited for different prognostic subgroups of patients with HER2+ disease. Within the node-negative population, OS for DCH and TCH were found to be high (>95%), despite some imbalance in the number of T1 and T2 tumors. Slight discrepancies in age were balanced by equivalence in menopausal status. As a result of improvements in the treatment of HER2+ breast cancer, the landscape for treatment of low-risk HER2+ tumors has shifted toward chemotherapy de-escalation. In a recent single-arm phase II study by Tolaney et al,[14] single-agent paclitaxel given for 12 weeks in combination with 1 year of adjuvant trastuzumab (APT trial) for small node-negative tumors demonstrated very low recurrence rates with favorable toxicity profiles. Similar results were seen in the single-arm phase II trial using DCH by Jones et al.[13]

Within HER2+, node-positive populations, comparison of FEC-DH with either AC followed by taxane/trastuzumab or TCH in the adjuvant setting has never been performed despite frequent use, phase III evidence,[18] and inclusion in recent ASCO guidelines.[16] In the sentinel BCIRG-006 trial, AC-TH compared with TCH was found to be associated with higher DFS (80% vs 78%) but not OS in the final 10-year analysis.[15] Similarly, for patients with node-positive breast cancer in our study, no significant difference in OS was seen for FEC-DH relative to TCH, yet OS was improved for patients with hormone receptor–positive, HER2+ disease (98.3% vs 91.6%).

An evolving body of literature supports biological differences in estrogen receptor–positive (ER+)/HER2+ compared with ER–/HER2+ breast cancer.[19,20] Coamplification of *TOP2A* is more common in ER+/HER2+ than ER–/HER2+ disease and could contribute to selective anthracycline benefit.[21] Furthermore, HER2 may be a less important driver in hormone receptor–positive[22] breast malignancies, making combination anthracycline/taxane chemotherapy more relevant. Interestingly, when survival was evaluated for hormone receptor–negative tumors, the opposite was true, with TCH appearing to have higher survival relative to FEC-DH (90.8% vs 83.3%) despite lacking statistical power. In the neoadjuvant phase II TRYPHAENA trial,[23] similar results were seen, with higher pathologic complete response (pCR) rates in ER–/HER2+ tumors treated with TCH + pertuzumab (84%) versus FEC-DH + pertuzumab (65%). Yet, for ER+/HER2+ tumors receiving the same chemotherapy, rates

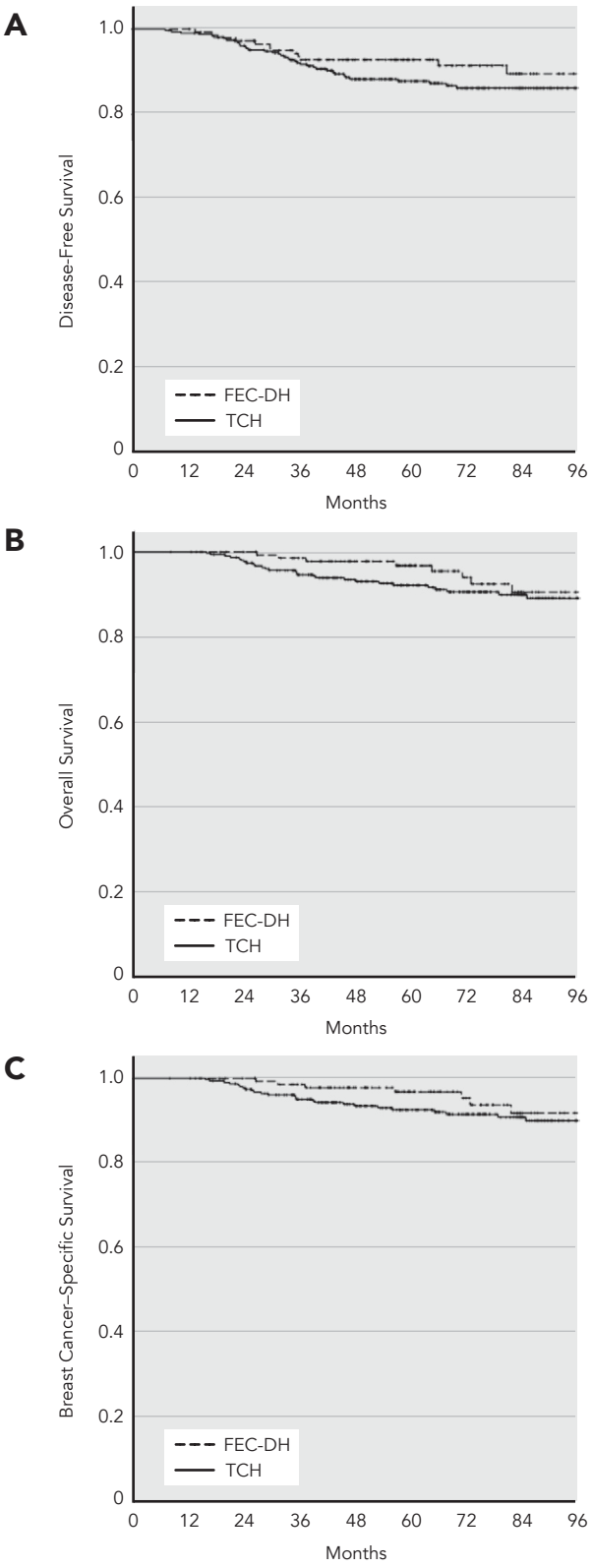

Figure 4. Kaplan-Meier plots for (A) disease-free survival, (B) overall survival, and (C) breast cancer–specific survival for the node-positive cohort. Abbreviations: FEC-DH, fluorouracil/epirubicin/cyclophosphamide followed by docetaxel/trastuzumab; TCH, docetaxel/carboplatin/trastuzumab.

of pCR were similar (50% vs 49%). Patients achieving a total (axillary and breast) pCR had higher 3-year DFS rates than those without a pCR (HR, 0.27).[24] Similar results have been reported in other neoadjuvant trials.[25]

The addition of other anti-HER2 agents to trastuzumab-based chemotherapy regimens has shown additional benefit in the adjuvant setting. However, these agents are not universally available or accepted without long-term survival data, and therefore the results of this study can still be considered relevant in the current era. In the phase III APHINITY trial,[26] patients were randomly allocated to receive trastuzumab-based chemotherapy with or without pertuzumab starting with the first cycle of taxane-containing chemotherapy and continuing for up to 18 cycles. Although most patients were treated with an anthracycline-containing regimen (FEC-DH or AC-TH), TCH was permitted. The addition of pertuzumab to standard treatment revealed a statistically significant, albeit small, absolute improvement in invasive DFS (absolute benefit of 1.8%) at 3 years.[26] In the phase III ExteNET study, patients were randomized to neratinib versus placebo for 1 year following completion of trastuzumab-based adjuvant chemotherapy. Neratinib also yielded a small absolute benefit in invasive DFS events[27] but with significant grade 3 diarrhea in 40% of patients. In preplanned subgroup analyses, patients with node-positive or hormone receptor–negative disease derived greater benefit with the addition of pertuzumab.[26] Conversely, patients with hormone receptor–positive disease derived greater benefit with the addition of neratinib.[27] Final OS analyses for both APHINITY and ExteNET are awaited. NCCN[28] and ASCO[16] guidelines now consider trastuzumab + pertuzumab an option in the adjuvant setting for node-positive disease, and extended anti-HER2 therapy with neratinib in patients with node-positive and hormone receptor–positive disease. Of note, the benefits and toxicities of extended anti-HER2 therapy with neratinib after pertuzumab exposure are unknown.

Given the retrospective design of our study, we were unable to capture all potential covariates that may have impacted treatment assignment and/or outcomes. First, whether performance status or particular comorbidities influenced choice of adjuvant chemotherapy is unknown. We were only able to measure and control for the U-CCI. Within our study, >95% of patients had a U-CCI score of 0 to 1, indicating relatively low levels of comorbidity, and U-CCI interaction was found to be nonsignificant in multivariable testing for OS and BCSS.

Second, we did not measure completion rates of adjuvant trastuzumab. In the ShortHER clinical trial,[29] 9 weeks of adjuvant trastuzumab failed to reach a noninferiority end point compared with 12 months (HR, 1.15, with 95% CIs crossing the upper boundary of 1.289). In a

Table 5. Multivariable Analysis of Overall Survival

	Node-Negative Cohort (A)			Node-Positive Cohort (B)		
Patient Variables	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Chemotherapy						
TCH		Ref			Ref	
DCH (A)/FECDH (B)	1.956	0.707–5.410	.196	1.900	0.851–4.239	.117
Menopausal status						
Postmenopausal		Ref			Ref	
Premenopausal	0.392	0.127–1.215	.105	0.608	0.307–1.205	.154
U-CCI						
0		Ref			Ref	
≥1	0.945	0.262–3.415	.932	0.793	0.302–2.078	.637
Tumor grade						
2		Ref			Ref	
3	1.262	0.411–3.877	.684	1.780	0.620–5.107	.284
LVI						
Absent		Ref			Ref	
Present	1.177	0.407–3.408	.764	1.568	0.660–3.727	.309
T stage						
T1		Ref				
T2	1.887	0.727–4.897	.192	1.925	0.767–4.831	.163
T3	NA	NA	NA	2.107	0.623–7.123	.231
N stage						
N1					Ref	
N2	–	–	–	2.314	1.077–4.971	.032[a]
N3	–	–	–	1.948	0.789–4.809	.148
Hormone receptor status						
ER+/PR+		Ref			Ref	
ER–/PR–	2.100	0.790–5.583	.137	1.210	0.589–2.487	.604
Radiotherapy						
Yes		Ref			Ref	
No	1.226	0.470–3.201	.677	1.157	0.331–4.043	.820

Abbreviations: DCH, docetaxel/cyclophosphamide; ER, estrogen receptor; HR, hazard ratio; LVI, lymphovascular invasion; NA, not applicable; PR, progesterone receptor; TCH, docetaxel/carboplatin/trastuzumab; U-CCI, updated Charlson comorbidity index.
[a]*P*<.05.

subgroup analysis of ShortHER by nodal status, noninferiority cutoffs were met for node-negative tumors. Moreover, with the favorable toxicity profile of trastuzumab and universal funding within the Canadian healthcare system, most oncologists are diligent in the administration of a complete course.

Another limitation of our study was the lack of prospective toxicity data. In our node-positive cohort, use of an anthracycline should ideally be weighed against longer-term cardiac morbidity. However, <2% of patients in the node-positive cohort had a preexisting cardiac arrhythmia or history of congestive heart failure at baseline, as assessed by the treating radiation or medical oncologist's consultation reports (data not shown). Further limiting patient comorbidity as a factor in survival analyses is that approximately 98% of patients had a score of 0 to 1 on the U-CCI, indicative of a relatively healthy population.

Conclusions

Overall, this study provides valuable information with respect to the management of HER2+ breast cancer by further substantiating de-escalation of chemotherapy in the node-negative population while validating the effectiveness of FEC-DH in the node-positive population.

Submitted March 8, 2018; accepted for publication July 30, 2018.

Disclosures: The authors have disclosed that they have not received any financial considerations from any person or organization to support the preparation, analysis, results, or discussion of this article.

Author contributions: *Study concept:* Veitch, King, Tang, Lupichuk. *Data acquisition:* Veitch, Khan. *Oversight and coordination of data management:* Kostaras. *Data cleaning:* Veitch, Tilley. *Data analysis:* Tilley, Kostaras. *Data interpretation:* Veitch, Tilley, Ribnikar, Kostaras, King, Tang, Lupichuk. *Manuscript preparation:* Veitch, Kostaras. *Manuscript editing:* Khan, Tilley, Ribnikar, King, Tang, Lupichuk. *Final approval:* Veitch, Lupichuk.

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