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ORIGINAL REPORT

High-Dose Chemotherapy With Autologous Stem-Cell Support As Adjuvant Therapy in Breast Cancer: Overview of 15 Randomized Trials

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ABSTRACT

Purpose
Adjuvant high-dose chemotherapy (HDC) with autologous hematopoietic stem-cell transplantation (AHST) for high-risk primary breast cancer has not been shown to prolong survival. Individual trials have had limited power to show overall benefit or benefits within subsets.

Methods
We assembled individual patient data from 15 randomized trials that compared HDC versus control therapy without stem-cell support. Prospectively defined primary end points were relapse-free survival (RFS) and overall survival (OS). We compared the effect of HDC versus control by using log-rank tests and proportional hazards regression, and we adjusted for clinically relevant covariates. Subset analyses were by age, number of positive lymph nodes, tumor size, histology, hormone receptor (HmR) status, and human epidermal growth factor receptor 2 (HER2) status.

Results
Of 6,210 total patients (n = 3,118, HDC; n = 3,092 control), the median age was 46 years; 69% were premenopausal, 29% were postmenopausal, and 2% were unknown menopausal status; 49.5% were HmR positive; 33.5% were HmR negative, and 17% were unknown HmR status. The median follow-up was 6 years. After analysis was adjusted for covariates, HDC was found to prolong relapse-free survival (RFS; hazard ratio [HR], 0.87; 95% CI, 0.81 to 0.93; $P < .001$) but not overall survival (OS; HR, 0.94; 95% CI, 0.87 to 1.02; $P = .13$). For OS, no covariates had statistically significant interactions with treatment effect, and no subsets evinced a significant effect of HDC. Younger patients had a significantly better RFS on HDC than did older patients.

Conclusion
Adjuvant HDC with AHST prolonged RFS in high-risk primary breast cancer compared with control, but this did not translate into a significant OS benefit. Whether HDC benefits patients in the context of targeted therapies is unknown.

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INTRODUCTION

In the 1980s and 1990s, thousands of patients with breast cancer were treated with high doses of chemotherapy followed by bone marrow transplantation or autologous hematopoietic stem-cell transplantation.[1] The major driver of the high-dose chemotherapy (HDC) movement was the preclinical rationale that predicted greater cytotoxicity for increasing dose-intensity. Chemotherapy is known to reduce tumor burden, so administering as high doses as possible would seem to be optimal.[2] However, the National Surgical Adjuvant Breast and Bowel Project showed that outcomes were not improved by increasing the dose of cyclophosphamide from 600 to 1,200 mg/m^2, nor from 1,200 to 1,800 and 2,400 mg/m^2.[3,4] The US Intergroup showed that increasing the dose of doxorubicin from 60 to 75 or 90 mg/m^2 did not improve relapse-free survival (RFS) or overall survival (OS).[5]

Published reports of nonrandomized comparisons of HDC with adjuvant therapy not having stem-cell support (ie, control group) were encouraging,[6] but the findings arose from potentially large

patient selection biases, including different staging in the two groups. Women with breast cancer and advocates began demanding HDC. By 1995, autologous bone marrow transplantation was being used in the treatment of more occurrences of breast cancer than of any other type of cancer, mostly outside of clinical trials.

Initial reports of randomized, clinical trials of HDC appeared in 1999. Since then, there have been 15 known randomized trials for high-risk primary breast cancer that compared control groups with HDC plus autologous hematopoietic stem-cell transplantation as adjuvant therapy.[7-21] The generally accepted conclusion from these trials has been negative (ie, that HDC has little or no benefit over control regarding OS).

A primary objective of this study was to address whether the conclusion that HDC is no better than control therapy is correct. In view of the individual trial reports, no overview could conclude that adjuvant HDC dramatically prolongs OS in primary breast cancer. However, the open question of whether HDC prolongs survival at all remains. Answering the question is complicated, because HDC is not a single regimen; the 15 trialists employed heterogeneous mixes of drugs, schedules, and doses. Moreover, the control regimens used in the trials also varied; some trialists used no therapy (ie, zero dose), and others used standard regimens containing agents not part of the trial HDC regimen.

Our second major objective was to address whether subsets of patients with primary breast cancer benefit from adjuvant HDC. The importance of evaluating treatment variability in subsets of patients with breast cancer was firmly established over a period of years and was supported by research in the 1970s through the 1990s. Knowledge accumulating during this time about the chemotherapy responsiveness of breast cancer suggested associations between such responsiveness and patient age,[22,23] as well as tumor characteristics of hormone-receptor status,[24-26] grade,[26,27] and lymph node involvement.[28] Evidence in support of HDC effect became available after the randomized trials were initiated.[29-32] Some investigators proposed that younger women benefit from HDC,[11] and others suggested that human epidermal growth factor receptor 2 (HER2) –negative tumors are sensitive to increasing dose.[12,18] But individual trials have little power for distinguishing benefits within subsets of patients, because such analyses are subject to well-known subset biases.[33]

We addressed both major objectives by assembling a database that contained individual patient results of the 15 known randomized trials of adjuvant breast cancer. We specified the patient subsets in our institutional review board–approved protocol.

METHODS

The trial selection process we used is illustrated in Figure 1 and is described in the Appendix (online only). We assessed 15 randomized trials involving patients with primary high-risk breast cancer who were randomly assigned to HDC versus control therapy in the adjuvant setting between 1990 and 2002. We collected patient-level data from each study that included clinical characteristics, treatments, and outcomes, and we worked with the various trialists to merge the individual patient data into a single database. Details of the regimens used and of the demographic and clinical characteristics of patients in each of the studies we evaluated are listed in Tables 1 and 2.

The primary end points were RFS and OS. RFS was defined as the time from surgery to disease recurrence or death as a result of any cause.[39] OS was defined as the time from surgery to death as a result of any cause. We evaluated

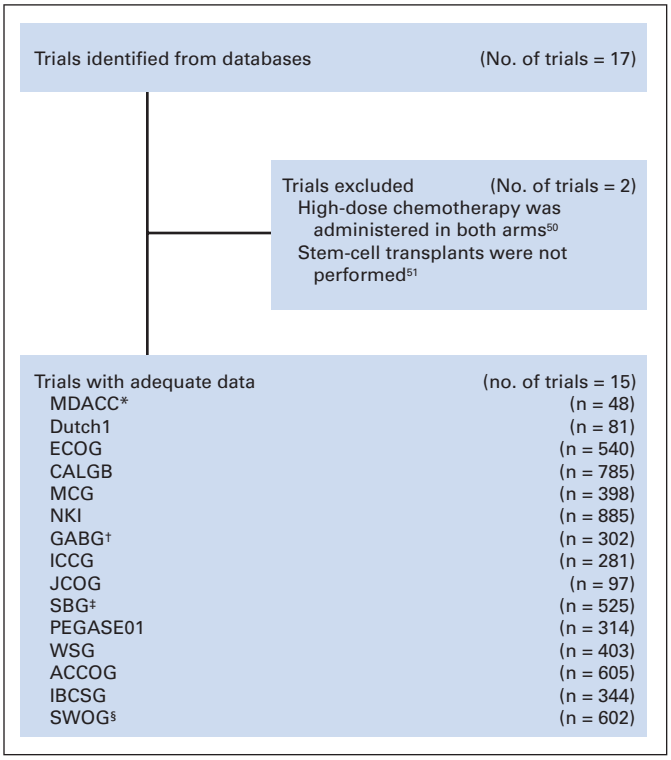

Fig 1. Study selection process. (*) Thirty patients were excluded because they received neoadjuvant therapy rather than adjuvant therapy. (†) Five patients were excluded because of a lack of cooperation after random assignment. (‡) This trial was excluded from The Cochrane Collaboration review,[52] because the study evaluated two experimental therapies and did not include a control group receiving conventional-dose chemotherapy; also noted, patients with bony micrometastases were not excluded from the study. (§) The 2007 *Journal of Clinical Oncology* publication[21] for this trial included only 536 patients. This tiral was excluded from The Cochrane Collaboration review,[52] because it was ongoing and the data were immature. ACCOG, Anglo-Celtic Cooperative Oncology Group; CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; GABG, German Adjuvant Breast Cancer Study Group; IBCSG, International Breast Cancer Study Group; ICCG, International Collaborative Cancer Group; JCOG, Japan Clinical Oncology Group; MCG, Michelangelo Cooperative Group; MDACC, MD Anderson Cancer Center; NKI, the Netherlands Cancer Institute; PEGASE01, Programme d'évaluation des greffes autologues dans le cancer du sein; SBG, Scandinavian Breast Group; SWOG, Southwest Oncology Group; WSG, West German Study Group.

the results for both end points by using the Kaplan-Meier product limit method, and we compared the results across treatment groups by using the log-rank test. Additionally, we considered RFS and OS within patient subsets defined by age (< 50 *v* ≥ 50 years), number of positive lymph nodes (≥ 10 *v* $<$ 10), tumor size (≥ 2 *v* < 2 cm), histology (invasive ductal *v* invasive lobular), hormone receptor status (estrogen- or progesterone-receptor positive *v* both negative), and HER2 status (positive *v* normal). In view of the multiplicities of subset analyses, we provided these analyses without *P* values or CIs. We used Cox proportional hazards regression models to assess the outcome of HDC versus control after the analysis was adjusted for trial, age, number of positive lymph nodes (square root transformation), and hormone receptor status (including a category for missing status). We provided the hazard ratio (HR) of HDC to control and its 95% CI (on the basis of the likelihood ratio) for RFS and OS for each of the 15 trials as well as overall.

Because the 15 trials used a variety of drugs and dose-intensities for the HDC and control regimens, we converted to dose-intensity by using the method of Hryniuk.[40,41] This method determines the average weekly dose-intensity (the summation dose-intensity [SDI]) and the total dose-intensity over both the induction phase and the treatment phase (the summation dose intensity product [SDIP]). The SDI and SDIP for each trial are listed in Table

Table 1. Trial and Patient Characteristics

Trial	Year of First Accrual	Year of Publication	Total No. of Patients	Follow-Up (years)	Median Age (years)	Induction Regimen	HDC Regimen	Control Regimen	SDI			SDIP		
									HDC	Control	Difference	HDC	Control	Difference
MDACC	1990	2000,[7] 2006[34]	48*	7	46	1,000 F, 50 D, 500 C	5,250 C, 1,200 Et, 165 P over 3 days 2 cycles	No additional chemotherapy	2.32	2.07	0.25	70	50	20
Dutch1	1991	1998,[8] 2002[35]	81	6	47	500 F, 120 E, 500 C	6,000 C, 480 T, 1,600 Cb over 4 days	No additional chemotherapy	3.13	2.10	1.03	47	25	22
ECOG	1991	2003[9]	540	7	44	1,400 C, 60 D, 1,000 F	6,000 C, 800 T over 4 days	No additional chemotherapy	2.25	2.10	0.15	68	50	18
CALGB	1991	2005[10]	785	9	45	600 C, 60 D, 1,200 F	5,625 C, 165 P, 600 BCNU over 3 days	900 C, 90 P, 90 BCNU over 3 days	2.16	1.90	0.26	52	36	16
MCG	1993	2001[11]	398	7	44	—	7,000 C, 8,000 Mt, 240 E, 600 T, 160-180 A	120 E 3 cycles then 600 C, 40 Mt, 600 F 6 cycles	2.76	1.81	0.95	50	60	−10
NKI	1993	2003[12]	885	8	46	500 F, 90 E, 500 C	6,000 C, 480 T, 1,600 Cb over 4 days	500 F, 90 E, 500 C (1 additional cycle)	2.72	1.70	1.02	49	25	24
GABG	1993	2004,[13] 2008[36]	302	5	48	90 E, 600 C	6,000 C, 600 T, 40 M over 4 days	1,000 C, 80 Mt, 1,200 F 3 cycles (28 days)	2.23	1.66	0.57	41	40	1
ICCG	1993	2005[14]	281	4	47	cycle 1: 600 F, 50 E, 600 C; cycles 2 and 3: 1,200 F, 50 E, 1200 C	6,000 C, 500 T, 800 Cb	1,200 F, 50 E, 1,200 C 2 additional cycles (28 days)	2.21	1.39	0.82	38	33	5
JCOG	1993	2008[15]	97	7	47	500 C, 40 D, 500 F	6,000 C, 600 T	No additional chemotherapy	1.80	1.56	0.24	43	28	15
SBG	1994	2000[16] 2007[37]	525	6	48	HDC only: 600 C, 60 E, 600 F 3 cycles	6,000 C, 500 T, 800 Cb over 4 days	Doses individually tailored, 6 plans. Start dose: 600 F, 75 E, 900 C, 9 cycles (21 days)	2.33	1.86	0.47	35	50	−15
PEGASE 01	1994	2005[17]	314	5	48	500 F, 100 E, 500 C	120 mg/kg C, 45 M, 140 A	No additional chemotherapy	2.98	1.82	1.16	54	22	32
WSG	1995	2005[18]	403	5	49	90 E, 600 C	3,000 C, 90 E 400 T every 28 days	600 C, 40 Mt, 600 F 3 cycles (14 days)	2.78	2.10	0.68	33	29	4
ACCOG	1995	2004[19]	605	6	45	75 D	4,000 C single dose then 6,000 C, 800 T over 4 days	600 C, 50 Mt, 600 F 8 cycles (21 days)	2.48	1.62	0.86	47	58	−11
IBCSG	1995	2006,[20] 2009[38]	344	5	47	—	4,000 C, 200 E 3 cycles (21 days)	600 C, 90 E or 60 D 4 cycles (21 days), then 1,400 C, 1,200 F, 80 Mt over 14 days 3 cycles (28 days)	4.73	1.84	2.89	42	44	−2
SWOG	1996	2007[21]	602	8	46	HDC only: 80 D, 600 C	STAMP I: C, P, BCNU or STAMP V: C, Cb, T	80 D: 3 cycles (14 days) then 200 Pac: cycles (14 days) then 3,000 C 3 cycles (14 days)	3.00	2.50	0.50	36	45	−9
Total			6,210	7					2.66	1.87	0.79	47	39.7	7.3

Abbreviations: A, melphalan; ACCOG, Anglo-Celtic Cooperative Oncology Group; BCNU, carmustine; C, cyclophosphamide; CALGB, Cancer and Leukemia Group B; Cb, carboplatin; D, doxorubicin; E, epirubicin; ECOG, Eastern Cooperative Oncology Group; Et, etoposide; F, fluorouracil; GABG, German Adjuvant Breast Cancer Study Group; HDC, high-dose chemotherapy; IBCSG, International Breast Cancer Study Group; ICCG, International Collaborative Cancer Group; JCOG, Japan Clinical Oncology Group; M, mitoxantrone; MCG, Michelangelo Cooperative Group; MDACC, MD Anderson Cancer Center; Mt, methotrexate; NKI, the Netherlands Cancer Institute; P, cisplatin; Pac, paclitaxel; PEGASE01, Programme d'évalution des greffes autologues dans le cancer du sein; SBG, Scandinavian Breast Group; SDI, summation dose intensity; SDIP, summation dose intensity product; STAMP I, Solid Tumor Autologous Marrow Transplant Program regimen I (C 1.85 g/m^2/d and P 55 mg/m^2/d, each for 3 days [days −6, −5, and −4], followed by BCNU 600 mg/m^2 [day−^{3}]); STAMP V, Solid Tumor Autologous Marrow Transplant Program regimen V (C 1.5 g/m^2/d, Cb 200 mg/m^2/d, and T 125 mg/m^2/d for 4 days (days −7 through −4); SWOG, Southwest Oncology Group; T, thiotepa; WSG, West German Study Group.

*Of the 78 total patients enrolled on this trial, 30 were randomly assigned to receive neoadjuvant therapy rather than adjuvant therapy; these patients were not included in the meta-analysis.

Table 2. Patient Demographic and Clinical Characteristics

Characteristic	HDC (n = 3,118) No.	HDC (n = 3,118) %	Control (n = 3,092) No.	Control (n = 3,092) %
Age, years				
Median	46.2		46	
Range	21.7-66.1		20.6-67.0	
Menopausal status				
Pre	2,146	68.8	2,134	69.0
Post	922	29.6	906	29.3
Missing	50	1.6	52	1.7
ER status				
Negative	1,024	32.8	1,043	33.7
Positive	1,415	45.4	1,382	44.7
Missing	679	21.8	667	21.6
PR status				
Negative	1,088	34.9	1,070	34.6
Positive	1,233	39.5	1,226	39.7
Missing	797	25.6	796	25.7
HmR status				
Negative	1,032	33.1	1,046	33.8
Positive	1,552	49.8	1,522	49.2
Missing	534	17.1	524	16.9
HER2 status				
Negative	648	20.8	612	19.8
Positive	220	7.1	215	7.0
Missing	2,250	72.2	2,265	73.3
Histologic grade				
Low	141	4.5	127	4.1
Medium	577	18.5	598	19.3
High	835	26.8	780	25.2
Missing	1,565	50.2	1,587	51.3
Histologic type				
Invasive ductal	1,227	39.4	1,215	39.3
Invasive lobular	242	7.8	257	8.3
Mixed	62	2.0	52	1.7
Other	108	3.5	104	3.4
Missing	1,479	47.4	1,464	47.3
Positive lymph nodes				
< 10	1,157	37.1	1,119	36.2
≥ 10	1,943	62.3	1,947	63.0
Missing	18	0.6	26	0.8
Tumor size, cm				
Median	3.0		2.7	
Range	0.01-17.5		0.03-20.0	
Assigned tamoxifen				
HmR negative				
No.	170	16.5	170	16.3
Total No.	1,032		1,046	
HmR positive				
No.	1,463	94.3	1,429	93.9
Total No.	1,551		1,522	
HmR missing				
No.	484	90.6	470	89.7
Total No.	534		524	

Abbreviations: HER2, human epidermal growth factor receptor 2; HDC, high-dose chemotherapy; HmR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor.

1 and are additionally defined in the Appendix. The analyses are based on intention to treat. All *P* values were based on two-sided tests, and significance was set at $P \leq .05$. Missing data for the covariates were multiply imputed,[42] but multiple imputation was not used for the subset analyses. *P* values were generated with the MIANALYZE procedure in SAS 9.1 (SAS Institute, Cary, NC). S-Plus, version 7.0 (Insightful Corporation, Seattle, WA), was also used to perform statistical analyses.

RESULTS

Of the 6,210 total patients included in these analyses, 3,118 were randomly assigned to HDC, and 3,092 were randomly assigned to control. The baseline characteristics of the two treatment groups were well balanced (Table 2). Relative to patients with primary breast cancer who receive adjuvant therapy, the women in these trials tended to be younger (median age, 46 years), to have larger tumors (median, 2.8 cm), and to have a greater number of positive axillary lymph nodes (median, 11). The rates of positivity of hormone receptor status and HER2 in this population were typical of high-risk breast cancer. Of patients with hormone receptor–positive tumors, 94% were treated with tamoxifen, with some variability across trials that ranged from 29% to 100%. The median follow-up was 6 years; 3,082 (50%) of the patients experienced disease recurrence, and 2,468 (40%) of the patients died.

RFS and OS Estimates of HDC Versus Control

HRs for OS and RFS and the corresponding 95% CIs are shown in Figures 2A and 2B for the individual trials. Eleven of the 15 trials showed a numerical reduction in the risk of recurrence for the HDC group; three trials statistically significantly favored HDC. Ten of the 15 trials showed a numerical reduction in the risk of death for the HDC group; results of one trial statistically significantly favored HDC.

Kaplan-Meier curves of the OS (Fig 3A), RFS (Fig 3B), and OS minus RFS (Fig 3C) for all trials combined are shown in Figure 3. The corresponding proportional hazards model results are shown in Table 3. After analysis was adjusted for trial, age, number of positive lymph nodes, and hormone receptor status, HDC was associated with a nonsignificant 6% reduction in the risk of death (HR, 0.94; 95% CI, 0.87 to 1.02; $P = .13$) and a significant 13% reduction in the risk of recurrence (HR, 0.87; 95% CI, 0.81 to 0.93; $P < .001$).

Kaplan-Meier curves of OS after disease recurrence are shown in Figure 3C. Patients in the HDC arm had a highly significant 16% increase in the risk of death after disease recurrence compared with patients in the control arm (HR, 1.16; 95% CI, 1.07 to 1.26; $P < .001$) after analysis was adjusted for trial, age, number of positive lymph nodes, and hormone receptor status.

Dose-Intensity and Dose-Intensity Product

The SDI and SDIP of the HDC and control arms of each trial are listed in Table 1. These values varied widely across trials, such that some control arms had larger SDIs or SDIPs than HDC arms in other trials. Figures 2C and 2D show the OS HRs and the corresponding 95% CIs for the individual trials plotted by the difference in SDI (Fig 2C) and the difference in SDIP (Fig 2D) between the two treatment arms. These plots show a positive trend with increasing dose-intensity. Multivariable analyses quantify this observation by considering SDI (and, separately, SDIP) as a substitute for HDC in the previously described multivariate analyses. After analysis was adjusted for trial, age, number of positive lymph nodes, and hormone receptor status status, an increasing SDI was associated with a statistically significant

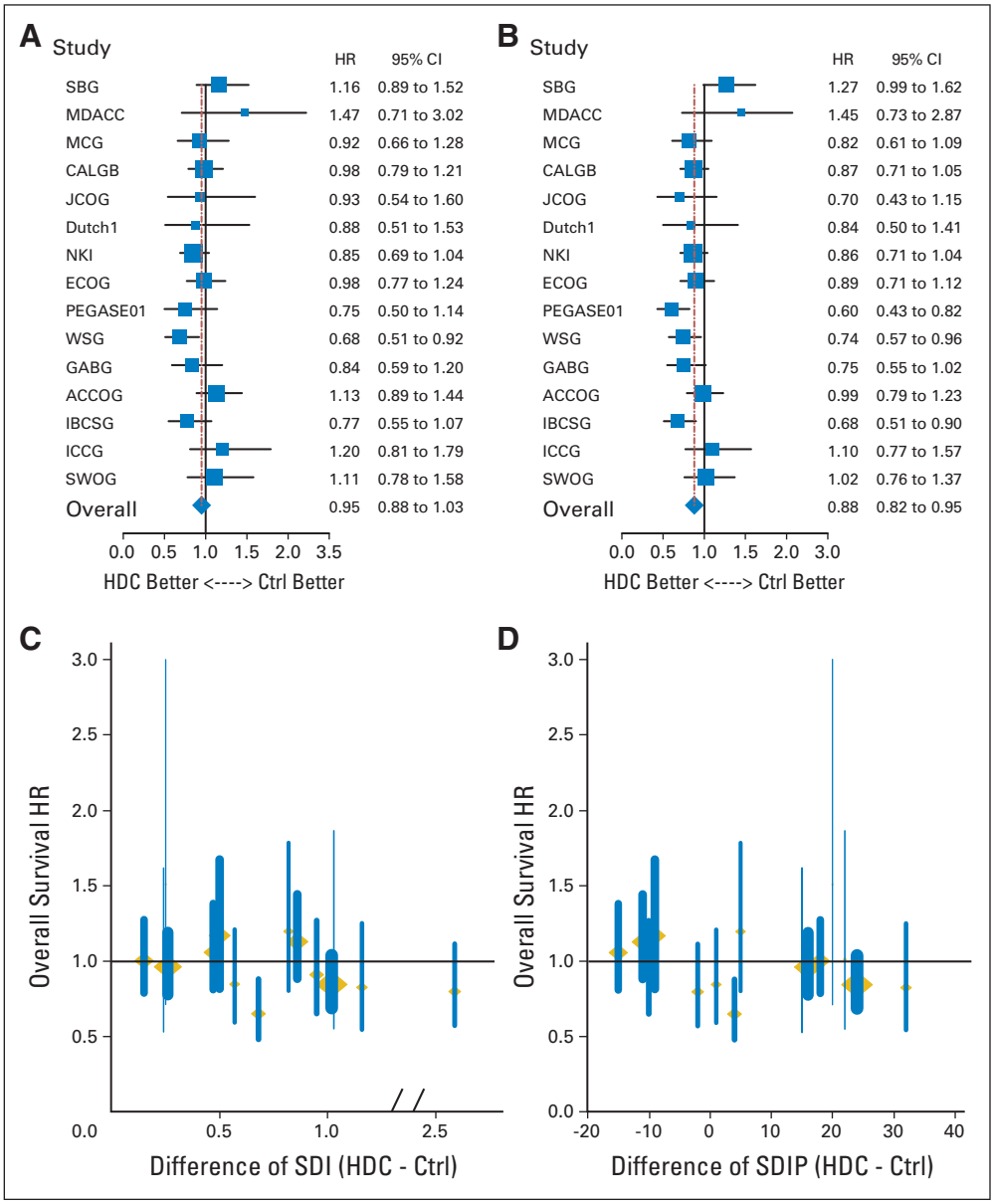

Fig 2. Comparison of hazard ratios (HRs) of high-dose chemotherapy (HDC) versus control (Ctrl) therapy and HRs plotted against the dose-intensity for each individual trial. For (A) overall survival (OS) and (B) relapse-free survival (RFS), the HR (solid squares) and 95% CIs (shown by whiskers on both sides of the solid squares) were derived by univariable Cox regression models (on the basis of the likelihood ratio). Adjusted HRs of death among patients on HDC versus control therapy plotted against (C) the differences in summation dose-intensity product (SDIP) between HDC and control treatment arms and (D) the differences in summation dose-intensity product (SDIP) between HDC and control treatment arms. ACCOG, Anglo-Celtic Cooperative Oncology Group; CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; GABG, German Adjuvant Breast Cancer Study Group; IBCSG, International Breast Cancer Study Group; ICCG, International Collaborative Cancer Group; JCOG, Japan Clinical Oncology Group; MCG, Michelangelo Cooperative Group; MDACC, M.D. Anderson Cancer Center; NKI, the Netherlands Cancer Institute; PEGASE01, Programme d'évaluation des greffes autologues dans le cancer du sein; SBG, Scandinavian Breast Group; SWOG, Southwest Oncology Group; WSG, West German Study Group.

reduction in the risk of both disease recurrence (for one unit increase: HR, 0.85; 95% CI, 0.80 to 0.92; $P < .001$) and death (HR, 0.91; 95% CI, 0.84 to 0.99; $P = .033$). SDIP was associated with a statistically significant reduction in the risk of disease recurrence (for 0.05 unit increase: HR, 0.85, 95% CI, 0.78 to 0.93; $P < .001$) and death (HR, 0.91; 95% CI, 0.82 to 1.00; $P = .045$).

Subset Analyses

Figure 4 shows the OS comparison of HDC versus control in prespecified subset analyses, as follows: age (Fig 4A: < 50 *v* ≥ 50 years), number of positive axillary lymph nodes (Fig 4B: ≥ 10 *v* $<$ 10), tumor size (Fig 4C: ≥ 2 *v* < 2 cm), histology (Fig 4D: invasive ductal *v* invasive lobular), hormone receptor status (Fig 4E: positive *v* negative), and HER2 status (Fig 4F: positive *v* normal). In view of the importance of tumor status for HER2 and hormone receptor in assessing chemotherapy effects in adjuvant breast cancer,[31] we also considered subsets defined by the joint hormone receptor and HER2 status (Fig 5). Because a high rate of missing data for HER2 status may lead to biased comparisons, we also considered patients who had unknown HER2 status.

We found that OS was not statistically different by treatment arm in any of the subgroups except for women with HER2-negative disease, for whom there was a 21% reduction in the risk of death (Fig 4F). The reduction was greatest (33%) among patients with both hormone receptor–negative and HER2-negative tumors—the so-called triple-negative breast cancer (Fig 5A). To address whether this observation is real, we compared patients who had hormone receptor–negative tumors and known HER2 status (Fig 5C) with those who had hormone receptor–negative tumors but unknown HER2 status (Fig 5F). The latter group showed little treatment effect, substantially less than those with hormone receptor–negative tumors for which HER2 status was available (Fig 5C).

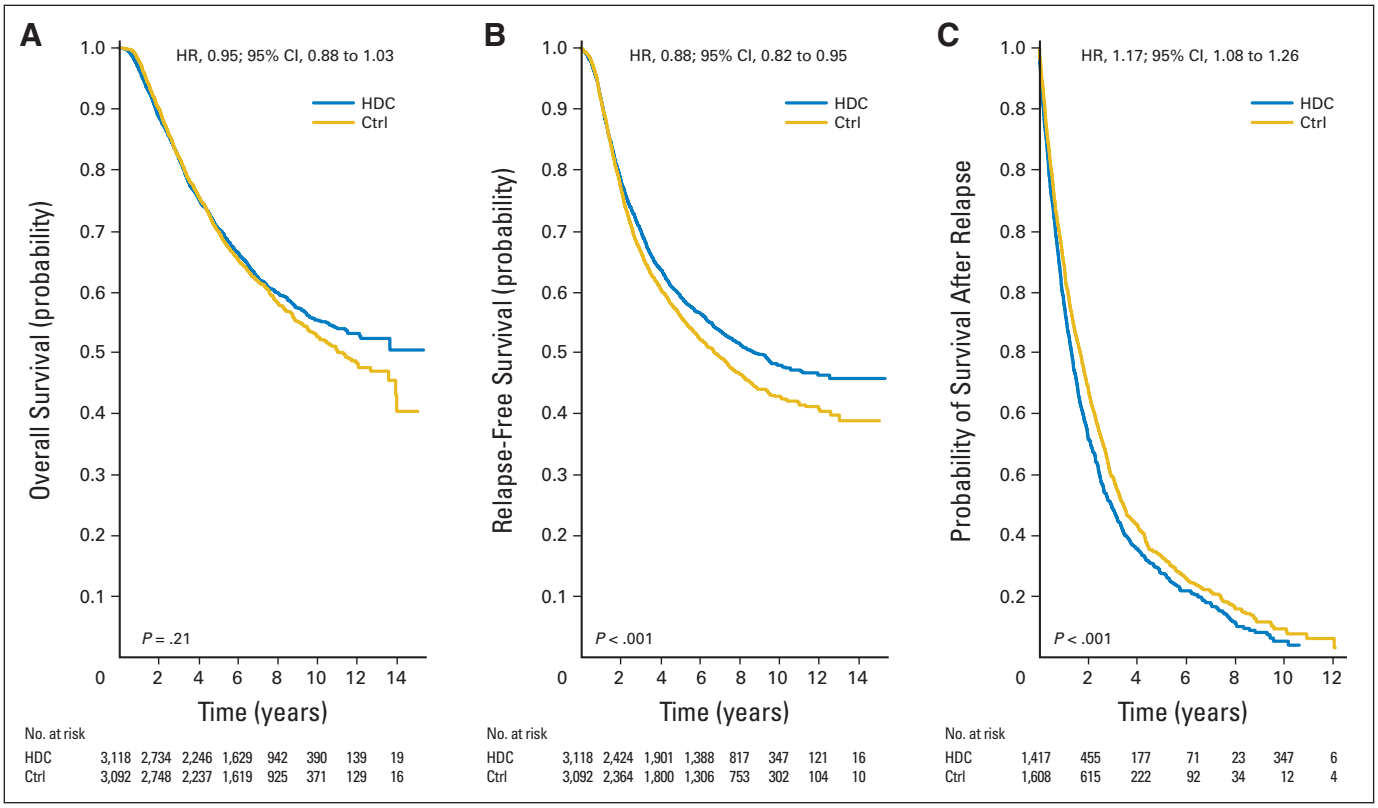

Fig 3. Kaplan-Meier estimates of survival outcomes. Hazard ratios (HRs) are presented with 95% CIs. *P* values are from the log-rank test. (A) Overall survival; (B) relapse-free survival; (C) probability of survival after relapse (overall survival − relapse-free survival). Ctrl, control; HDC, high-dose chemotherapy; OS, overall survival; RFS, relapse-free survival.

Toxicity Deaths and Secondary Malignancies

In six of the 15 trials there were a total of 33 secondary malignancies categorized as myelodysplastic syndrome or acute myelogenous leukemia. Of the 33, 17 occurred in the HDC arms, and 16 occurred in the control arms.

Of 89 total deaths attributed to toxicity, 72 (6.0%) occurred among the 1,207 deaths in the HDC arms, and 17 (1.4%) occurred among the 1,261 deaths in the control arms. To evaluate survival separate from treatment-related mortality, we conducted an additional analysis that excluded patients whose deaths were attributed to toxicity. The HR was 0.90 (95% CI, 0.83 to 0.99; $P = .011$) for OS after analysis was adjusted for trial, age, hormone receptor status, and number of positive lymph nodes.

Table 3. Cox Proportional Hazards Model Treating Missing HmR Status As a Separate Category and Using Multiple Imputation for Other Missing Covariates While Treating Age As Categoric

Variable	OS			RFS		
	HR	95% CI	*P*	HR	95% CI	*P*
HDC *v* control	0.94	0.87 to 1.02	.13	0.87	0.81 to 0.93	< .001
Age ≥ 50 years *v* < 50 years	0.97	0.89 to 1.06	.55	0.91	0.84 to 0.98	.019
HmR status positive *v* negative	0.59	0.54 to 0.64	< .001	0.68	0.63 to 0.73	< .001
Square root of positive lymph nodes	1.28	1.22 to 1.34	< .001	1.26	1.20 to 1.31	< .001

Abbreviations: HDC, high-dose chemotherapy; HmR, hormone receptor; HR, hazard ratio; OS, overall survival; RFS, relapse-free survival.

DISCUSSION

In a literature-based meta-analysis of 13 randomized trials, Farquhar et al[43] found a statistically significant benefit for event-free survival but not for OS. Banna et al[44] reviewed solid tumor trials and concluded that there was no overall benefit for the use of HDC. However, they suggested that additional trials could consider HDC in patients with triple-negative primary breast tumors, because there were no targeted therapies for these patients. Pedrazolli et al[45] reviewed 14 randomized trials in solid tumors and supported the evaluation of regimens of HDC with low mortality rates in future breast cancer trials for subgroups most likely to benefit; a retrospective study by Rodenhuis et al[46] suggested that such a subgroup include patients with HER2-normal tumors.

The largest individual studies had statistical power to detect a 30% improvement in survival outcomes.[47] Our study had 80% power to detect a 10% improvement in RFS and a 12% improvement in OS. Our analyses showed that, compared with patients who were randomly assigned to receive control, those who were randomly assigned to receive HDC had a 13% improvement in RFS. Curiously, OS after disease recurrence (ie, OS minus RFS) was significantly worse in the HDC group (Fig 3C). As a consequence, the apparent RFS benefit translated to only a 6% improvement in OS.

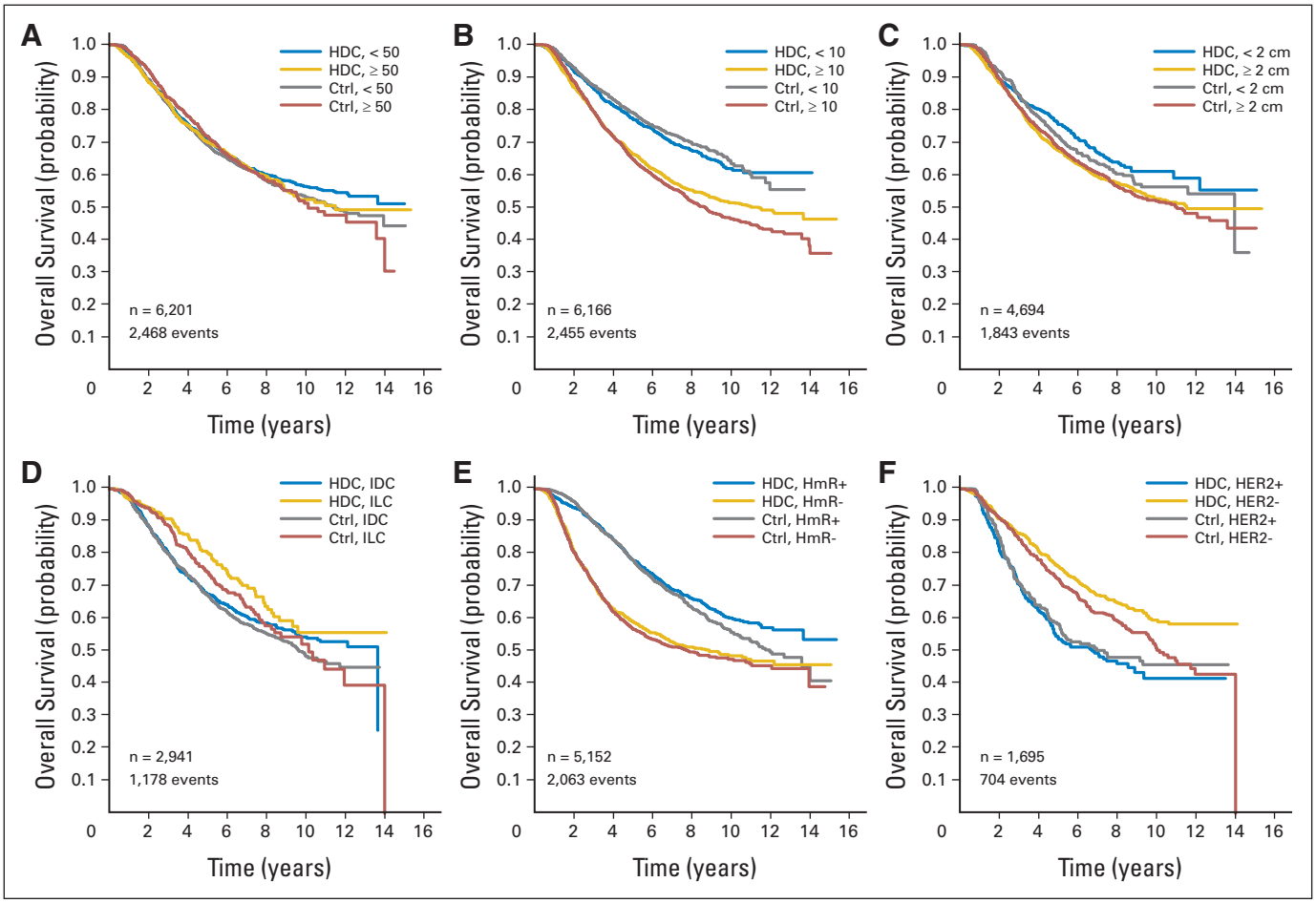

Fig 4. Kaplan-Meier estimates of overall survival (OS) comparison of high-dose chemotherapy (HDC) and control (Ctrl) therapy in prespecified subset analyses. Subsets of (A) patient age in years; (B) number of positive lymph nodes; (C) tumor size; (D) tumor histology; (E) tumor hormone receptor status (HmR); and (F) human epidermal growth factor receptor 2 status (HER2). IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

In our experience, it is unusual to observe a significant benefit in RFS for one treatment group and then a significant benefit in OS after recurrence (ie, OS minus RFS) for the other group. There are several possible explanations. These studies were not blinded, so it is possible that some investigators assessed recurrence more diligently in the control group, perhaps fearing that they were most at risk of recurrence. Perhaps postrecurrence therapy was less feasible for the patients who were randomly assigned to HDC, whether as a result of residual toxicity, unwillingness of the patient to receive additional therapy, or exclusion from eligibility of clinical trials of targeted agents, such as trastuzumab or aromatase inhibitors. It is also possible that HDC reduces measurable disease burden but that it has a less dramatic effect on latent but insidious disease harbored in bone marrow, for example.

Our analyses by SDI and SDIP are revealing. They evince a dose response that extends into the high doses considered in these trials. However, the effect is not sufficiently clear to translate into clinical practice.

In clinical decision making, any benefit in recurrence or survival must be weighed against the greater toxicities of HDC. Individual studies have reported that the quality of life among patients receiving HDC is lower during treatment than that among the patients receiving control.[43] There is less agreement regarding quality of life once treatment is complete. Farquhar et al[43] reported that quality of life becomes comparable in the two groups over time, whereas Marino et al[48] reported that physical functioning, role functioning, fatigue, and pain were negatively affected by HDC both during treatment and 1 year later.[48]

Individual studies have suggested that age, hormone receptor status, or HER2 expression may be predictive of the benefits of HDC. Our analyses showed that the only apparently significant OS benefit was among patients with HER2-negative tumors, and additionally, among patients with triple-negative tumors. However, only approximately 27% of the tumors had HER2 status available. (Anti-HER2 therapy was not available during this era and was specifically excluded for trials of HDC.) When broken out by HER2 status, we found that HDC is unlikely to show much of a benefit in triple-negative tumors. After analysis was adjusted for the missing data, we concluded that the triple-negative observation is likely to be spurious.

A limitation of our analysis is that we combined data that were highly heterogeneous, and variations exist among the patient populations, among the HDC regimens, and among the control regimens and also exist in dose-intensity differences between the HDC and control arms across the 15 trials. Indeed, the dose-intensity of the control arm was greater than that of the HDC arm in some of the trials

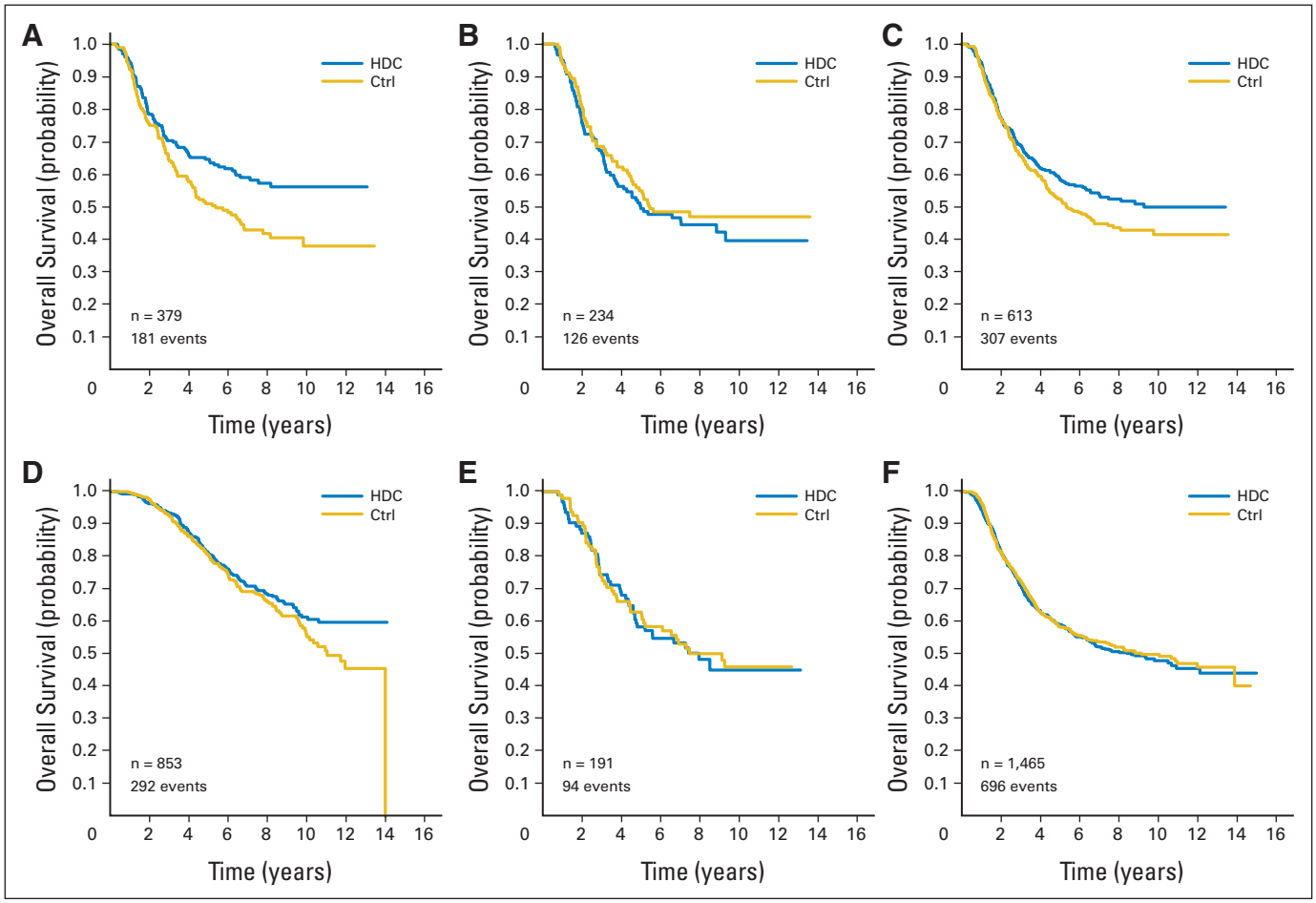

Fig 5. Kaplan-Meier estimates of overall survival comparison of high-dose chemotherapy (HDC) and control (Ctrl) therapy in subsets of patients defined by hormone receptor (HmR) status and human epidermal growth factor receptor 2 (HER2) status. (A) HmR negative, HER2 negative; (B) HmR negative, HER2 positive, (C) HmR negative, HER2 either positive or negative (known); (D) HmR positive, HER2 negative; (E) HmR positive, HER2 positive; (F) HmR negative, HER2 unknown.

and for some measures of intensity. For example, the SDIP for control was greater than that for HDC (difference < 0) in five trials (Table 1). These trials compared arms with different agents and not just differences in dose. Excluding these five trials effects a modest change in the HR of HDC versus control for OS of 0.90 (95% CI, 0.81 to 0.99; $P = .031$). Focusing on only the complementary set of trials, in the five with control arms that had more intensive doses, the HR was 1.03 (95% CI, 0.90 to 1.17; $P = .69$). Our adjustment for SDI and SDIP partially accounts for the differences in the treatment regimens, but no single number can perfectly measure the heterogeneity of the drug intensity of those regimens.

There are other differences in the trials as well, including that, although 94% of the patients with known hormone receptor–positive tumors were assigned tamoxifen, this proportion varied across the trials from 29% to 100%. We additionally adjusted for trial differences by incorporating patient-level covariates and by including an indicator of trial in the multivariate analyses.

An obvious caveat to our conclusions is that they apply for the settings of the 15 known randomized trials and the regimens considered. The relative benefits of HDC for other treatment regimens and in combination with targeted therapies for the treatment of breast cancer remain unknown.

Our conclusion in this article, that HDC does not have a statistically significant benefit in OS, is supported by the conclusion in our companion manuscript,[49] that HDC does not have a statistically significant benefit in OS in metastatic breast cancer. Both studies leave open the possibility of a modest reduction in the hazards of OS in the range of 5% to 10%, but neither was able to identify subsets of patients who may benefit from HDC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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