Table 1 Characteristics of study populations

	Japanese living in Nagano, Japan	Japanese Brazilians living in São Paulo, Brazil	Non-Japanese Brazilians living in São Paulo, Brazil	*P* for difference
Number of participants	185	44	134	
Mean age (±SE), yr	62.8 (0.40)	63.8 (0.82)	63.6 (0.47)	0.37
P[a]	0.31	Reference	0.84	
Family history of breast cancer, *n* (%)	17 (9.2)	5 (11.4)	14 (10.5)	0.92
P[a]	0.68	Reference	0.98	
History of benign breast disease, *n* (%)	11 (6.0)	4 (9.1)	8 (6.0)	0.46
P[a]	0.65	Reference	0.62	
Mean age at first menarche (±SE), yr	13.9 (0.12)	13.2 (0.26)	13.3 (0.15)	<0.01
P[a]	<0.01	Reference	0.75	
Mean age at menopause (±SE), yr	50.0 (0.34)	50.8 (0.69)	48.2 (0.40)	<0.01
P[a]	0.29	Reference	<0.01	
Nulliparous, *n* (%)	17 (9.2)	5 (11.4)	15 (11.2)	0.55
P[a]	0.58	Reference	0.81	
Number of births (more than four births), *n* (%)[b]	6 (3.6)	12 (30.8)	57 (47.9)	<0.01
P[a]	<0.01	Reference	<0.01	
Mean age at first birth (±SE), yr[b]	26.2 (0.34)	26.5 (0.72)	23.6 (0.41)	<0.01
P[a]	0.65	Reference	<0.01	
Breast feeding (yes), *n* (%)[b]	154 (93.3)	35 (89.7)	107 (89.9)	0.72
P[a]	0.27	Reference	0.61	
Mean height (±SE), cm	152.9 (0.43)	151.8 (0.89)	157.1 (0.52)	<0.01
P[a]	0.29	Reference	<0.01	
Mean body mass index (±SE), kg/m^2	23.4 (0.28)	24.7 (0.57)	27.0 (0.34)	<0.01
P[a]	0.04	Reference	<0.01	
Smoking (ever smoker), *n* (%)	6 (3.3)	7 (15.9)	38 (28.4)	<0.01
P[a]	<0.01	Reference	<0.01	
Alcohol drinking (drinker), *n* (%)	67 (36.2)	5 (11.4)	25 (18.7)	<0.01
P[a]	<0.01	Reference	0.63	
Physical activity in past 5 years (yes), *n* (%)	85 (46.5)	19 (43.2)	26 (19.4)	<0.01
P[a]	<0.01	Reference	<0.01	

[a]*P* values for comparison with Japanese Brazilians living in São Paulo, Brazil; [b]Among parous women only.

and they smoked more and were taller and physically less active than the other two populations. Japanese Brazilians had an earlier menarche, more births and greater BMI, and they smoked more, drank less and were physically less active than Japanese, but they had later ages at menopause and first birth, fewer births and lower BMI, and they smoked less and were shorter and physically more active than non-Japanese Brazilians.

Because of an insufficient amount of sampled blood, we did not measure the levels of the following hormones: estradiol for 17 participants; bioavailable estradiol, estrone or SHBG for two participants each; or androstenedione for one participant. The proportion of participants with levels below the LOD were 0.9% for estradiol, 3.6% for estrone, 0% for bioavailable estradiol and SHBG, 0.6% for androstenedione and DHEAS, 24% for testosterone and 69% for free testosterone.

Adjusted hormone levels varied significantly across the three populations for all hormones (Table 2). Japanese Brazilians had significantly higher levels of estradiol, bioavailable estradiol, estrone, testosterone and free testosterone, and lower SHBG levels, than Japanese, whereas levels of androstenedione and DHEAS did not differ between the two populations (Table 2). Similar results were seen for analyses stratified by BMI (under and over 25), except for androstenedione level, which did not differ between Japanese Brazilians and Japanese whose BMI was under 25, but androstenedione level was significantly lower among Japanese Brazilians than among Japanese whose BMI was over 25 (Table 3).

Table 2 Adjusted geometric mean hormone levels in three populations[a]

	Japanese living in Nagano, Japan	Japanese Brazilians living in São Paulo, Brazil	Non-Japanese Brazilians living in São Paulo, Brazil	*P* for difference
Estradiol, pg/mL				
Age-adjusted	9.0	13.8	15.5	<0.01
(95% CI)	(8.6 to 9.4)	(12.5 to 15.3)	(14.6 to 16.5)	
P[a]	<0.01	Reference	0.052	
Multivariate[b]	9.7	14.3	15.5	<0.01
(95% CI)	(8.7 to 10.9)	(12.5 to 16.4)	(14.0 to 17.1)	
P[a]	<0.01	Reference	0.28	
Bioavailable estradiol, %				
Age-adjusted	23.1	30.6	22.9	<0.01
(95% CI)	(22.1 to 24.1)	(28.0 to 33.4)	(21.7 to 24.1)	
P[a]	<0.01	Reference	<0.01	
Multivariate[b]	23.7	30.2	20.6	<0.01
(95% CI)	(21.6 to 26.0)	(27.0 to 33.8)	(19.0 to 22.3)	
P[a]	<0.01	Reference	<0.01	
Estrone, pg/mL				
Age-adjusted	23.0	40.3	34.1	<0.01
(95% CI)	(22.0 to 24.0)	(36.8 to 44.1)	(32.4 to 35.9)	
P[a]	<0.01	Reference	<0.01	
Multivariate[b]	23.8	41.1	33.3	<0.01
(95% CI)	(21.5 to 26.3)	(36.5 to 46.3)	(30.6 to 36.4)	
P[a]	<0.01	Reference	<0.01	
Sex hormone-binding globulin, nM/L				
Age-adjusted	74.1	54.3	60.2	<0.01
(95% CI)	(69.4 to 79.1)	(47.5 to 62.0)	(55.8 to 65.1)	
P[a]	<0.01	Reference	0.18	
Multivariate[b]	68.4	53.0	70.7	0.01
(95% CI)	(59.5 to 78.5)	(44.9 to 62.4)	(62.6 to 79.7)	
P[a]	<0.01	Reference	<0.01	
Androstenedione, ng/mL				
Age-adjusted	0.65	0.56	1.04	<0.01
(95% CI)	(0.60 to 0.70)	(0.47 to 0.66)	(0.95 to 1.15)	
P[a]	0.12	Reference	<0.01	
Multivariate[b]	0.73	0.60	1.00	<0.01
(95% CI)	(0.61 to 0.88)	(0.48 to 0.76)	(0.85 to 1.18)	
P[a]	0.06	Reference	<0.01	
DHEAS, μg/dL				
Age-adjusted	50.6	58.0	44.5	0.03
(95% CI)	(46.3 to 55.4)	(48.2 to 69.8)	(40.0 to 49.4)	
P[a]	0.19	Reference	0.01	
Multivariate[b]	57.2	63.1	46.7	0.04
(95% CI)	(46.6 to 70.2)	(49.4 to 80.6)	(39.2 to 55.8)	
P[a]	0.38	Reference	0.02	
Testosterone, ng/mL				
Age-adjusted	0.02	0.11	0.18	<0.01
(95% CI)	(0.02 to 0.03)	(0.07 to 0.17)	(0.14 to 0.24)	
P[a]	<0.01	Reference	0.06	
Multivariate[b]	0.03	0.10	0.14	<0.01
(95% CI)	(0.02 to 0.04)	(0.06 to 0.20)	(0.09 to 0.22)	
P[a]	<0.01	Reference	0.38	
Free testosterone, pg/mL				

Table 2 Adjusted geometric mean hormone levels in three populations[a] *(Continued)*

Age-adjusted	0.21	0.39	0.44	<0.01
(95% CI)	(0.19 to 0.23)	(0.33 to 0.46)	(0.40 to 0.48)	
P^a	<0.01	Reference	0.18	
Multivariate[b]	0.22	0.39	0.39	<0.01
(95% CI)	(0.19 to 0.26)	(0.32 to 0.47)	(0.34 to 0.45)	
P^a	<0.01	Reference	0.92	

DHEAS, dehyroepianrosterone sulfate; 95% CI, 95% confidence interval; [a]*P* values for comparison with Japanese Brazilians living in São Paulo, Brazil; [b]Adjusted for age (continuous), age at first menarche (continuous), age at menopause (continuous), number of births (0, 1, 2 or 3, 4+), age at first birth (≤22, 23 to 26, ≥27 yr, nulliparous), height (continuous), body mass index (continuous), smoking (never smokers, past smokers, current smokers), alcohol drinking (nondrinkers, occasional drinker, regular drinkers), and physical activity in past 5 years (no, ≤2 days/wk, ≥3 days/wk).

Japanese Brazilians had significantly higher levels of bioavailable estradiol, estrone and DHEAS, and lower levels of SHBG and androstenedione, than non-Japanese Brazilians. Levels of estradiol, testosterone and free testosterone, however, did not differ between Japanese Brazilians and non-Japanese Brazilians (Table 2). Similar results were obtained when analyses were stratified by BMI (under and over 25), except for estrone and DHEAS. Levels of estrone were significantly higher among Japanese Brazilians than among non-Japanese Brazilians in individuals with a BMI under 25, but estrone levels did not differ between the two populations in individuals whose BMI was over 25, while DHEAS level did not differ regardless of BMI (under or over 25) (Table 3).

We further examined associations between endogenous sex hormone levels and known breast cancer risk factors or lifestyle factors (Table 4). BMI was significantly associated with higher estradiol, bioavailable estradiol, estrone, androstenedione, testosterone and free testosterone levels, as well as lower SHBG levels, but was not associated with DHEAS levels. Stratified analyses by study site (that is, the study in Nagano vs. the study in São Paulo) showed similar results for the two study sites. No statistically significant associations were observed between sex hormone levels and family history of breast cancer, history of benign breast disease, age at first menarche, age at menopause, parity, number of births, age at first birth, breast-feeding, height, smoking, alcohol drinking or physical activity during the past 5 years except for the following. We found a significantly higher level of SHBG among women who had a later age at menopause and among shorter women. We also observed a significantly higher level of DHEAS among women who had more births and a significantly lower level of testosterone among physically more active women. In stratified analyses by study site, however, we did not observe any findings which were consistent between the sites.

Discussion

In this cross-sectional study among postmenopausal Japanese, Japanese Brazilian and non-Japanese Brazilian women, we found significant differences in endogenous sex hormones among the three populations even after adjustment for known breast cancer risk factors. In particular, levels of estrogen and androgen in Japanese Brazilians were higher than levels in Japanese and were similar to or higher than levels in non-Japanese Brazilians. This pattern was observed for women with BMI values under and over 25. We also confirmed an increase in estrogen and androgen levels and a decrease in SHBG levels with increasing BMI.

As an initial comment, several methodological limitations of this study should be considered. First, our findings might be subject to the difference in study methods between Japan and Brazil, albeit that the two studies were conducted under a similar protocol. For example, we used serum samples for Japanese and plasma samples for both Japanese Brazilians and non-Japanese Brazilians. In this regard, we measured estrone levels in both serum and plasma from the same participants (n = 38). Although both levels were highly correlated (correlation coefficient = 0.94) and the percentage difference was relatively small (mean = -4%; 95% confidence interval, -9% to 1%), we used corrected values for the present study because the kit for estrone was applicable to serum samples only. Concurrently, we compared estrone levels among the three populations using crude values and observed the same results. The difference in blood samples is therefore unlikely to have affected the difference in sex hormone levels between the two populations. Given that blood collection methods also differed between the Japan and Brazil study sites, in addition to the types of blood samples used, we cannot exclude the possibility that our findings were affected by these differences. Another example is the difference in questionnaire data and data collection methods between Japan and Brazil. If such differences led to exposure misclassification, this might explain the observed absence of associations between sex hormone levels and known breast cancer risk factors or lifestyle factors. Second, although at least more than 96% of participants had detectable levels of estradiol, estrone, bioavailable estradiol, SHBG, androstenedione and DHEAS, the

Table 3 Adjusted geometric mean hormone levels[a] of three populations with stratification by body mass index[b]

	Japanese living in Nagano, Japan	Japanese Brazilians living in São Paulo, Brazil	Non-Japanese Brazilians living in São Paulo, Brazil	*P* for difference
Estradiol, pg/mL				
Low (BMI < 25)	9.5	14.2	15.0	<0.01
P[c]	<0.01	Reference	0.60	
High (BMI ≥25)	8.2	12.2	14.5	<0.01
P[c]	<0.01	Reference	0.06	
Bioavailable estradiol, %				
Low (BMI <25)	22.4	28.7	17.9	<0.01
P[c]	<0.01	Reference	<0.01	
High (BMI ≥ 25)	25.6	32.5	23.4	<0.01
P[c]	<0.01	Reference	<0.01	
Estrone, pg/mL				
Low (BMI < 25)	22.5	40.4	32.1	<0.01
P[c]	<0.01	Reference	<0.01	
High (BMI ≥25)	23.2	38.4	34.2	<0.01
P[c]	<0.01	Reference	0.19	
Sex hormone-binding globulin, nM/L				
Low (BMI < 25)	76.6	62.8	85.8	0.03
P[c]	0.04	Reference	<0.01	
High (BMI ≥25)	59.6	43.8	59.5	0.03
P[c]	0.02	Reference	0.02	
Androstenedione, ng/mL				
Low (BMI < 25)	0.64	0.63	0.91	0.03
P[c]	0.90	Reference	0.02	
High (BMI ≥25)	0.76	0.51	1.05	<0.01
P[c]	0.03	Reference	<0.01	
DHEAS, μg/dL				
Low (BMI < 25)	51.9	64.7	48.7	0.21
P[c]	0.13	Reference	0.11	
High (BMI ≥25)	54.6	52.2	43.4	0.29
P[c]	0.81	Reference	0.32	
Testosterone, ng/mL				
Low (BMI < 25)	0.01	0.07	0.13	<0.01
P[c]	<0.01	Reference	0.27	
High (BMI ≥25)	0.04	0.15	0.18	<0.01
P[c]	<0.01	Reference	0.69	
Free testosterone, pg/mL				
Low (BMI < 25)	0.18	0.32	0.31	<0.01
P[c]	<0.01	Reference	0.90	
High (BMI ≥25)	0.26	0.46	0.48	<0.01
P[c]	<0.01	Reference	0.85	

BMI, body mass index; DHEAS, dehyroepianrosterone sulfate; [a]Adjusted for age (continuous), age at first menarche (continuous), age at menopause (continuous), number of births (0, 1, 2 or 3, 4+), age at first birth (≤22, 23 to 26, ≥27, nulliparous), height (continuous), BMI (continuous), smoking (never smokers, past smokers, current smokers), alcohol drinking (nondrinkers, occasional drinkers, regular drinkers) and physical activity in the past 5 years (no, ≤2 days/wk, ≥3 days/wk); [b]The total participants in the low and high BMI groups were 199 and 156, respectively; [c]*P* values for comparison with Japanese Brazilians living in São Paulo, Brazil.

proportion of participants with levels below the LOD was relatively high for testosterone (24%) and free testosterone (69%). Our findings for testosterone and free testosterone should therefore be interpreted cautiously. Third, since our study included only a small number of Japanese Brazilians (n = 44), the findings might be due to chance and should be interpreted with caution.

We found higher circulating levels of estrogen and androgen in Japanese Brazilians than in Japanese, which were not accounted for by differences in the prevalence

Table 4 Adjusted geometric mean hormone levels by breast cancer risk factors and lifestyle-factors[a]

Breast cancer risk and lifestyle factors	Participants, *n*	Estradiol, pg/mL	Bioavailable estradiol, %	Estrone, pg/mL	Sex hormone-binding globulin, nM/L	Androstenedione, ng/mL	DHEAS, µg/dL	Testosterone, ng/mL	Free testosterone, pg/mL
Family history of breast cancer									
No	327	13.9	22.7	32.6	66.2	0.84	52.7	0.09	0.34
Yes	36	13.8	21.2	31.6	74.6	0.80	51.4	0.05	0.36
P for difference		0.90	0.18	0.57	0.12	0.66	0.83	0.08	0.40
History of benign breast disease									
No	339	13.9	22.6	32.5	66.9	0.84	52.9	0.09	0.34
Yes	23	14.3	22.0	33.5	69.0	0.78	52.1	0.08	0.31
P for difference		0.69	0.68	0.67	0.75	0.61	0.92	0.72	0.38
Age at first menarche, yr									
<12	101	13.7	22.9	31.6	66.7	0.83	49.5	0.08	0.33
13 or 14	166	13.9	22.2	32.4	65.2	0.83	54.8	0.09	0.34
15+	96	13.9	22.6	33.6	69.7	0.85	53.3	0.08	0.35
P for trend		0.81	0.81	0.18	0.51	0.78	0.43	0.99	0.60
P for trend[b]		0.70	0.47	0.30	0.24	0.68	0.29	0.83	0.39
Age at menopause, yr									
<48	116	14.0	23.0	32.6	64.5	0.89	57.0	0.08	0.34
49 to 51	108	14.0	22.0	33.1	70.2	0.78	51.6	0.09	0.34
52+	139	13.6	22.5	32.1	67.0	0.80	48.5	0.09	0.33
P for trend		0.47	0.65	0.68	0.57	0.20	0.05	0.66	0.75
P for trend[b]		0.80	0.06	0.93	0.02	0.32	0.51	0.59	1.00
Parity									
Parous	326	13.8	22.0	32.3	67.5	0.80	48.4	0.08	0.33
Nulliparous	37	13.7	23.3	32.9	67.2	0.87	58.0	0.10	0.34
P for difference		0.89	0.28	0.73	0.95	0.42	0.11	0.51	0.86
Number of births[c]									
1	32	13.7	20.6	32.8	69.6	0.77	43.7	0.10	0.30
2 or 3	219	13.4	22.2	31.6	67.8	0.79	43.9	0.08	0.32
4+	75	14.7	22.3	33.2	65.8	0.86	56.0	0.08	0.35
P for trend		0.27	0.26	0.71	0.55	0.38	0.046	0.76	0.20
Age at first birth[c], yr									
<22	79	13.2	21.3	31.5	70.9	0.80	44.0	0.09	0.31
23 to 26.9	138	13.9	21.5	33.1	68.1	0.78	46.7	0.07	0.33
27+	109	14.7	22.3	33.1	64.3	0.84	52.2	0.10	0.32
P for trend		0.09	0.29	0.52	0.16	0.47	0.11	0.40	0.89
P for trend[b]		0.10	0.32	0.53	0.37	0.58	0.39	0.47	0.81
Breast-feeding[c]									
No	27	14.3	23.2	33.5	63.4	0.82	46.9	0.09	0.33
Yes	296	13.7	21.9	32.2	67.6	0.81	47.2	0.08	0.32

Table 4 Adjusted geometric mean hormone levels by breast cancer risk factors and lifestyle-factors[a] *(Continued)*

P for difference		0.59	0.33	0.53	0.47	0.87	0.96	0.85	0.87
Height, cm									
<150.9	107	13.8	22.3	32.2	69.4	0.84	54.7	0.09	0.34
151 to 156.9	126	14.3	22.1	33.4	67.2	0.81	51.9	0.08	0.34
157+	124	13.7	23.2	32.2	63.8	0.85	51.7	0.09	0.34
P for trend		0.83	0.31	0.99	0.16	0.91	0.54	0.71	0.86
P for trend[b]		0.62	0.07	0.65	0.01	0.33	0.96	0.47	0.72
BMI, kg/m^2									
<24.9	199	13.3	20.9	31.1	75.3	0.77	51.1	0.07	0.30
25 to 29.9	116	14.5	24.2	32.2	60.2	0.79	48.4	0.09	0.34
30+	40	15.5	26.4	38.4	51.2	1.15	65.3	0.16	0.50
P for trend		0.01	<0.01	<0.01	<0.01	0.01	0.21	0.01	<0.01
P for trend[b]		<0.01	<0.01	<0.01	<0.01	<0.01	0.13	0.01	<0.01
Smoking									
Never smoker	310	13.2	24.3	32.0	62.9	0.80	53.5	0.09	0.35
Past smoker	37	13.6	23.7	32.4	62.3	0.77	51.4	0.06	0.38
Current smoker	14	14.9	20.0	33.2	76.3	0.94	52.8	0.12	0.29
P for difference		0.48	0.06	0.91	0.28	0.55	0.95	0.43	0.28
Alcohol drinking									
Nondrinker	266	14.0	22.0	32.7	69.9	0.85	49.4	0.10	0.34
Occasional drinker	39	14.1	23.5	32.4	63.7	0.82	59.1	0.08	0.34
Regular drinker	58	13.5	22.2	32.4	67.1	0.83	49.8	0.08	0.34
P for difference		0.76	0.48	0.97	0.42	0.89	0.29	0.48	0.98
Physical activity in past 5 years									
No	231	14.0	22.5	32.8	66.7	0.84	52.2	0.11	0.34
≤2 days/wk	63	13.8	22.1	32.1	67.5	0.79	50.6	0.05	0.33
≥3 days/wk	68	13.5	23.3	32.1	66.8	0.85	55.8	0.07	0.35
P for trend		0.46	0.48	0.58	0.95	0.97	0.56	0.02	0.60

DHEAS, dehyroepianrosterone sulfate; BMI, body mass index; [a]Adjusted for age (continuous), ethnic group (Japanese, Japanese Brazilians, non-Japanese Brazilians (Caucasian, mixed, Black), age at first menarche (continuous), age at menopause (continuous), number of births (0, 1, 2 or 3, 4+), age at first birth (≤22, 23 to 26, ≥27 yr, nulliparous), height (continuous), BMI (continuous), smoking (never smokers, past smokers, current smokers), alcohol drinking (nondrinkers, occasional drinkers, regular drinkers) and physical activity in the past 5 years (no, ≤2 days/wk, ≥3 days/wk); [b]Continuous variables; [c]Among parous women only.

of known breast cancer risk factors. This hormonal profile in Japanese Brazilians is consistent with the higher incidence and mortality rate of breast cancer in this population [4-6]. For instance, the age-adjusted incidence per 100,000 population for breast cancer among first-generation Japanese Brazilians from 1969 to 1978 was 24, while the incidences among Japanese from 1973 to 1977 were 12.7 in Osaka and 17.5 in Miyagi [4]. The standard mortality ratio for breast cancer among first-generation Japanese Brazilians from 1999 to 2001 on the basis of age-specific rates for Japanese in 2000 was 139 [5].

We also found higher circulating levels of bioavailable estradiol and estrone in Japanese Brazilians than in non-Japanese Brazilians, although levels of estradiol, testosterone and free testosterone did not significantly differ between the two populations. In the Multiethnic Cohort Study, Japanese Americans had significantly higher

estradiol levels than Caucasians and a slightly higher risk factor-adjusted incidence of breast cancer [10,18]. Although previous studies have shown lower incidence and mortality rates of breast cancer among Japanese Brazilians than among non-Japanese Brazilians [4-6], our findings suggest that the recent incidence and mortality rates among Japanese Brazilians might be similar to or higher than those of non-Japanese Brazilians.

The significant difference in sex hormone levels between Japanese Brazilians and Japanese might be determined by long-term exposure to environmental and lifestyle factors in Brazil. These differences were observed even after adjustment for known breast cancer risk factors, including BMI, which is a major determinant of estrogen levels in postmenopausal women. Although diet is one environmental factor that substantially differs between Japan and Brazil, the present study did not take into account dietary factors because we used different FFQ in the case-control studies in Nagano and São Paulo. Given that the report from the World Cancer Research Fund and American Institute for Cancer Research in 2007 showed no convincing or probable dietary risk factors for breast cancer [19], however, the difference in sex hormone levels between the two populations might not be explained by dietary factors only.

We observed an increase in estrogen and androgen levels and a decrease in SHBG levels with increasing BMI. Our findings are in general agreement with those of previous studies, and these associations have been consistently observed among both Asian and Western populations [10-13,15]. On the other hand, the determinants of sex hormone levels in postmenopausal women have not been firmly established, notwithstanding a relatively large number of epidemiological studies [10-14,16]. In the present study, we found a higher level of SHBG among women who had a later age at menopause and among shorter women. We also observed a higher level of DHEAS among women who had more births and a lower level of testosterone among physically more active women. In addition to the lack of consistency in these findings between the two study sites (that is, the study in Nagano vs. the study in São Paulo), our findings are inconsistent with those of previous studies, which found no significant associations among age at menopause, height and SHBG level, for example, or number of births and DHEAS level [12-14]. Higher physical activity levels were associated with lower levels of both estrogen and androgen [11,16], while another study reported no such association [10]. Given this lack of consistency with previous studies, our findings might be explained by multiple comparisons.

Conclusions

We found that levels of estrogen and androgen in Japanese Brazilians were higher than those in Japanese and similar to or higher than levels in non-Japanese Brazilians. Our findings may explain the previously observed increase in the incidence and mortality rate of breast cancer among Japanese Brazilians.

Abbreviations

BMI: body mass index; DHEAS: dehydroepiandrosterone sulfate; FFQ: food frequency questionnaire; IRMA: immunoradiometric assay; LOD: lower detection limit; SHBG: sex hormone-binding globulin.

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Author details

[1]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan. [2]Department of Surgery, Nagano Matsushiro General Hospital, Nagano, Japan. [3]Department of Breast and Thyroid Surgery, Nagano Red Cross Hospital, Nagano, Japan. [4]Department of Surgery, Nagano Municipal Hospital, Nagano, Japan. [5]Department of Surgery, Nagano Hokushin General Hospital, Nagano, Japan. [6]Nikkei Disease Prevention Center, São Paulo, Brazil. [7]Statistical Section/Head and Neck Surgery and Otorhinolaryngology Department, Hospital A.C. Camargo, São Paulo, Brazil. [8]Breast Surgery Department, Hospital A.C. Camargo, São Paulo, Brazil. [9]Department of Breast Surgery, Hospital Pérola Byington, São Paulo, Brazil. [10]Department of Breast Surgery, Hospital Santa Cruz, São Paulo, Brazil.

Authors' contributions

MI made substantial contribution to the conception and design of the study, as well as the analysis and interpretation of data, and was involved in drafting the manuscript. YK, SY, HO, HN, RK, GSH, INN, MSM, JM, FML and RA made substantial contributions to the study conception and design and the acquisition of data and were involved in critically revising the manuscript for important intellectual content. ST made substantial contributions to the study conception and design, as well as the analysis and interpretation of data, and was involved in critically revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

Safety of adjuvant trastuzumab for HER-2-overexpressing elderly breast cancer patients: a multicenter cohort study

Masataka Sawaki · Hirofumi Mukai · Nahomi Tokudome · Takahiro Nakayama · Naruto Taira · Toshiro Mizuno · Yutaka Yamamoto · Akiyo Horio · Toru Watanabe · Yukari Uemura · Yasuo Ohashi

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Abstract
Background For targeting anti-HER-2, trastuzumab-incorporated chemotherapy is the standard for HER-2-overexpressing breast cancer in adjuvant settings. But there are few data on trastuzumab in elderly patients. We evaluated the incidence of adverse events among an elderly population of trastuzumab-treated HER-2-positive breast cancer patients in adjuvant settings.
Methods Data on 39 elderly HER-2 overexpressing breast cancer patients treated with both curative surgery and adjuvant trastuzumab were retrospectively collected from a Japanese multicenter study. The loading dose was 8 mg/kg body weight, and the maintenance dose was 6 mg/kg every 3 weeks; or the loading dose was 4 mg/kg followed by 2 mg/kg weekly as maintenance.
Results After a median follow-up of 20.0 (2.4–53.9) months, a total of 32 patients (82.1%) completed 1-year trastuzumab treatment. The median treatment duration was 12.0 months (range 2–12; mean 10.5). Adverse events occurred in 11 patients (28.2%). Four (10.2%) discontinued or interrupted treatment after experiencing toxicity. One patient died because of interstitial pneumonia. Three patients (7.7%) had congestive heart failure (CHF), one of whom had a history of angina. Three patients (7.7%) had a lower left ventricular ejection fraction (LVEF), and brain natriuretic peptide elevation was totally observed in three patients (7.7%). Three patients with lower LVEF had received chemotherapy containing doxorubicin before trastuzumab. Of the three patients, two discontinued therapy

M. Sawaki (✉)
Department of Clinical Oncology and Chemotherapy, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
e-mail: m-sawaki@med.nagoya-u.ac.jp

H. Mukai
Department of Oncology and Hematology, National Cancer Center Hospital East, Chiba, Japan

N. Tokudome
Department of Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

T. Nakayama
Department of Breast and Endocrine Surgery, Osaka University Hospital, Osaka, Japan

N. Taira
Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan

T. Mizuno
Department of Medical Oncology, Mie University Hospital, Tsu, Japan

Y. Yamamoto
Department of Breast and Endocrine Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

A. Horio
Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

T. Watanabe
Department of Medicine, Hamamatsu Oncology Center, Hamamatsu, Shizuoka, Japan

Y. Uemura · Y. Ohashi
Department of Biostatistics, School of Public Health, University of Tokyo, Tokyo, Japan

because of CHF, but all recovered with proper medication containing a diuretic agent.
Conclusions Elderly patients tolerated trastuzumab well, although careful management is needed.

Keywords Breast cancer · HER-2/*neu* · Trastuzumab · Elderly

Introduction

The human epidermal growth factor receptor 2 (HER-2) protein is a unique and useful target for antibody therapy against breast cancers overexpressing the HER-2/*neu* gene. HER-2 is overexpressed in 15–25% of human breast cancers [1–3] and correlates with poor clinical prognosis in women with both node-positive and node-negative disease [4–6]. Overexpression of HER-2 has also been associated with potentially more aggressive tumors. As an anti-HER-2-targeting treatment, trastuzumab with chemotherapy is a standard adjuvant systemic therapy for HER-2-positive primary breast cancer [7–10]. However, trastuzumab treatment is also associated with cardiac dysfunction and congestive heart failure (CHF) [11–15]. Recently, a long-term assessment in the herceptin adjuvant (HERA) trial found that the incidence of cardiac endpoints remained low [16]. On the other hand, there have been few data on trastuzumab treatment in elderly patients because in these pivotal adjuvant clinical trials all patients had received standard chemotherapy according to the inclusion criteria. Cardiac toxicity associated with anthracycline-containing chemotherapy in older women with breast cancer is well known [17, 18], so caution is necessary for elderly patients. Thus, we sought to evaluate the incidence of adverse events in an elderly population of HER-2-positive breast cancer patients treated with trastuzumab in an adjuvant setting.

Patients and methods

The data on 39 elderly (≥69 years) HER-2 overexpression breast cancer patients who had been treated with both curative surgery and adjuvant trastuzumab from January 2006 to February 2009 were retrospectively collected from a Japanese multicenter study. The patients did not have cardiac symptoms, uncontrolled hypertension, uncontrolled arrhythmia, or coronary artery disease in practical settings.

Adjuvant chemotherapy had been given according to the investigators' preference. Patients diagnosed with hormone-receptor-positive neoplasia were given endocrine therapy. Radiation therapy was performed in patients who had undergone breast-conserving surgery.

HER-2 status was determined by immunohistochemical (IHC) staining or amplification on fluorescence in situ hybridization (FISH). IHC scores of 3+ or FISH positive (ratio of HER-2:CEP17 ≥2) were regarded as positive. The loading administration dose of trastuzumab was 8 mg/kg of body weight, and the maintenance dose was 6 mg/kg every 3 weeks. Alternatively, the loading dose was 4 mg/kg followed by 2 mg/kg weekly as a maintenance dose. Cardiac function was determined by the left ventricular ejection fraction (LVEF) on echocardiography during trastuzumab treatment. The schedule of cardiac monitoring including brain natriuretic peptide (BNP) during the treatment was not defined. CHF was defined by symptoms, physical signs and objective findings; it included an LVEF drop of 10% or a drop to an absolute LVEF of 50% by the obtained echocardiogram. The severity of adverse events (AEs) was evaluated by the use of the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 3.0). Patients were monitored for clinical effects and drug-related AEs.

Results

Patients

Table 1 shows the characteristics of 39 patients. The mean age was 72.3 (69–84). As adjuvant chemotherapy, 27

Table 1 Patient characteristics ($n = 39$)

Mean age, years (range)	72.3 (69–84)
Primary stage	
I	8
II	25
III	6
Histological grade	
1	6
2	3
3	29
unknown	1
Hormone receptor	
ER (+) and/or PgR (+)	12
ER (−) and PgR (−)	27
Adjuvant chemotherapy	
Anthracyclines and taxanes	6
Anthracyclines, no taxanes	19
Taxanes, no anthracyclines	1
CMF	1
No cytotoxic chemotherapy	12
Adjuvant hormone therapy	
Aromatase inhibitor	11
Tamoxifen	1
No	27

patients (69.2%) had sequential chemotherapy. Of those, 25 (92.6%) had an anthracycline-containing regimen. For six of these patients, this consisted of FEC/FAC: fluorouracil 500 mg/m^2, epirubicin 75–100 mg/m^2, doxorubicin 40–60 mg/m^2, and cyclophosphamide 500 mg/m^2 every 3 weeks for more than four cycles; or AC: doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles and taxane (paclitaxel or docetaxel). In 19 patients, the anthracycline-containing regimens included the following. One patient had CMF (cyclophosphamide 100 mg orally on days 1 to 14, methotrexate 40 mg/m^2 on days 1 and 8 intravenously, and fluorouracil 600 mg/m^2 intravenously on days 1 and 8, every 4 weeks for six cycles); one had TC (docetaxel 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles; and 12 patients (30.8%) had trastuzumab therapy without chemotherapy.

Safety and tolerability

After a median follow-up time of 20.0 (2.4–53.9) months, a total of 32 patients (82.1%) had completed receiving trastuzumab for 1 year. The median duration of treatment was 12.0 months (range, 2 to 12 months; mean, 10.5 months). Two patients (5.1%) are continuing treatment because they have not completed 1 year; three patients (7.7%) discontinued treatment because of toxicity; one patient (2.6%) had interrupted treatment because of toxicity but was reintroduced after recovery; one patient (2.6%) discontinued after relapse. Adverse events are shown in Tables 2 and 3. Adverse events occurred in 11 patients (28.2 %). One patient died after toxicity led to interstitial pneumonia (IP). She had been undergoing hormone therapy (anastrozole) with trastuzumab after irradiation for the breast. In the CT scan the density of pneumonia was detected almost in accordance with the irradiation area. From the autopsy, it was diagnosed as IP that had been induced by neither infection nor carcinomatous lymphangiosis. The cause of IP was not specified and not significantly related to trastuzumab, although it should not always be denied directly. Three patients (7.7%) had CHF, 2 of whom complained of systemic edema, and 3 had dyspnea. One of these three CHF patients had a history of angina. In particular, regarding cardiotoxicity examinations, three patients (7.7%) had lower LVEF, of whom two also had elevated BNP. BNP elevation was totally observed in three patients (7.7%). Three patients with lower LVEF had been receiving chemotherapy containing doxorubicin immediately prior to the initiation of trastuzumab treatment. Two of the three patients with lower LVEF were discontinued because of CHF, but all recovered with proper medication containing a diuretic agent.

We here present a case of CHF in a 70-year-old female diagnosed with left breast cancer: T1c, N1, M0, stage IIA. Her pathology was estrogen-receptor-positive, progesterone-receptor-negative, and HER-2-positive (3+; IHC). She had received FAC neoadjuvant chemotherapy (the doxorubicin cumulative dose was 260 mg/m^2), followed by 12 courses of weekly paclitaxel. The points of EF and BNP before chemotherapy were 64% and 12.1 pg/ml, respectively. The cardiothoracic ratio (CTR) was 51.3% (Fig. 1a). After she completed chemotherapy, she underwent surgery, after which she received tamoxifen and irradiation for the chest wall, supraclaviculares, and parasternal lymph nodes. After completion of irradiation, trastuzumab treatment was begun. At this time, the point of EF was 73%. The loading administration dose of trastuzumab was 8 mg/kg body weight, and the maintenance dose was 6 mg/kg every 3 weeks. After three cycles of trastuzumab, she experienced dyspnea and leg edema. The point of EF was decreased from 73 to 53%, BNP was

Table 2 Adverse events ($n = 39$)

Events	Grade (G); patients (%)
Acute infusion reaction	G1; 6 (15.4)
Edema	G1; 1, G2; 1 (5.1)
Dyspnea	G1; 1, G3; 2 (7.7)
Rash	G1; 1, G2; 1 (5.1)
Nail change	G1; 2 (5.1)
Interstitial pneumonia	G5; 1 (2.6)
Left ventricular systolic dysfunction	G1; 1, G3; 2 (7.7)
Elevated brain natriuretic peptide	3 (7.7)

Table 3 Adverse events (grade 2–5)

Age	Chemotherapy	Trastuzumab treatment	Cardio-toxicity	Ejection fraction (%)	Pulmonary-toxicity	Duration of trastuzumab (months)
76	None	Tri-weekly	None	62–67	Interstitial pneumonia	2
77	None	Tri-weekly	CHF[a]; G3	69–68	None	5
71	CAF (ADM 300 mg/m^2)	Tri-weekly	CHF[a]; G3	70–49	None	8
70	CAF (ADM 260 mg/m^2), weekly PTX	Tri-weekly	CHF[a]; G2	73–53	None	2

[a] Congestive heart failure

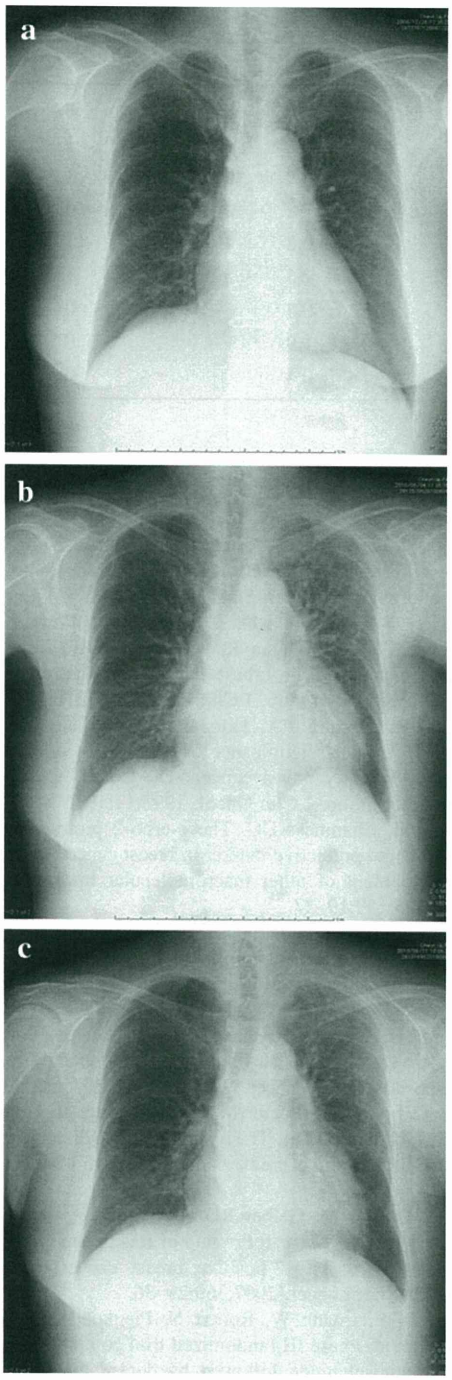

Fig. 1 **a** The points of EF and BNP before chemotherapy were 64% and 12.1 pg/ml, respectively. The cardiothoracic ratio (CTR) was 51.3%. **b** After three cycles of trastuzumab, our patient had dyspnea and leg edema. The point of EF was decreased from 73 to 53%, BNP was elevated from 12.1 to 40.7 pg/ml, and CTR was 60.5%. **c** After 1 week, her heart function had recovered, the point of CTR had decreased from 60.5 to 54.8%, and BNP had also decreased from 40.7 to 9.3 pg/ml

elevated from 12.1 to 40.7 pg/ml, and the CTR was 60.5% (Fig. 1b). She was diagnosed with heart failure (grade 2) by a cardiologist and given a diuretic agent, furosemide (80 mg/day). After 1 week, her heart function had recovered, the point of CTR had decreased from 60.5 to 54.8%, and the BNP had also decreased from 40.7 to 9.3 pg/ml (Fig. 1c). Trastuzumab was reintroduced after LVEF recovery without any other problems.

Outcomes

Of the 39 patients, 2 (5.1%) died; 1 of these deaths was caused by IP, while the other was non-breast cancer-specific deaths. Thirty-six patients (92.3%) were free of relapse, and one had distant metastasis. All patients who completed 1 year of treatment have experienced no more cardiotoxicity or other adverse events.

Discussion

Treatment of breast cancer with trastuzumab is complicated by cardiotoxicity [19]. Cardiac safety in major adjuvant trials is shown in Table 4. The incidence of cardiac endpoints after a long-term assessment in the HERA trial was recently reported. The incidence of discontinuation of trastuzumab because of cardiac disorders was low (5.1%), that of severe CHF was 0.8%, and that of confirmed significant LVEF decreases was 3.6% [16]. In the other pivotal studies [10, 20, 21], the cardiac event rate was highest in the anthracycline-containing trastuzumab patients (1.9–3.8%) and lowest in patients who had received the regimen of docetaxel, carboplatin, and trastuzumab (TCH) (0.4%). But there are not enough data available on trastuzumab treatment in elderly patients. Thus, it was necessary to evaluate the incidence of adverse events, in particular cardiotoxicity, in an elderly population of HER-2-positive breast cancer patients.

Although the patient population in this study was small, we presented safety data on trastuzumab for elderly breast cancer patients. Overall, the incidence of adverse events was low. Only four patients (10.2%) discontinued treatment because of toxicity. Three patients (7.7%) had CHF, but all recovered with proper medication containing a diuretic agent. As for the treatment for heart failure (HF) caused by trastuzumab-induced cardiotoxicity, in most patients it is reversible [19, 22–25]. LVEF improves after trastuzumab withdrawal and with, or sometimes without, the initiation of HF therapy [19]. Although the identification of patients at risk for trastuzumab-induced cardiotoxicity and the prediction of LVEF recovery have never been investigated, recently troponin 1 was found to be a predictive risk factor for cardiotoxicity, and patients with troponin 1 elevation were unlikely to recover from cardiac dysfunction despite HF therapy [19].

Table 4 Cardiac safety in the four major adjuvant trials

Trial	ARM	Baseline LVEF (%)	CHF[a] (%)	Cardiac death (*n*)
HERA [16]	H 1 year	≥55	0.6	0
	Nil		0	1
NSABP B-31 [21]	AC → P	≥50	0.9	1
	AC → PH		3.8	0
N9831 [20]	AC → P	≥50	0.2	1
	AC → PH		2.5	1
BCIRG 006 [10]	AC → D	≥50	0.4	0
	AC → DH		1.9	0
	D Carbo H		0.4	0

[a] Congestive heart failure

Trastuzumab is indicated for HER-2-positive patients according to the ASCO/CAP guideline [26]. Especially for elderly patients, there is clinical significance to demonstrating the benefit of trastuzumab without toxicity induced by chemotherapy. We have thus been investigating clinical positioning between trastuzumab monotherapy and a combination of trastuzumab and chemotherapy based on a randomized controlled trial in women aged over 70 years with HER-2-positive primary breast cancer [27]. Our hypothesis is that the trastuzumab monotherapy group is not inferior to the trastuzumab and chemotherapy group in disease-free survival, and is superior in safety and health-related quality of life; these are registered as protocol ID: UMIN000002349 for the University Hospital Medical Information Network (UMIN) and protocol ID: NCT01104935 for ClinicalTrials.gov. To prepare this multicenter study, we collected trastuzumab treatment data to ascertain the feasibility of this treatment for elderly patients.

In summary, elderly patients tolerated trastuzumab well, although careful management is needed. Prospective data on a larger number of elderly patients are needed in order to confirm the safety of trastuzumab treatment in elderly patients.

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Conflict of interest The authors state that they have no conflict of interest.

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Clinical Trial Notes

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Evaluation of Trastuzumab Without Chemotherapy as a Post-operative Adjuvant Therapy in HER2-positive Elderly Breast Cancer Patients: Randomized Controlled Trial [RESPECT (N-SAS BC07)]†

Masataka Sawaki[1,*], Nahomi Tokudome[2], Toshiro Mizuno[3], Takahiro Nakayama[4], Naruto Taira[5], Hiroko Bando[6], Shigeru Murakami[7], Yutaka Yamamoto[8], Masahiro Kashiwaba[9], Hiroji Iwata[10], Yukari Uemura[11] and Yasuo Ohashi[11]

[1]Department of Clinical Oncology and Chemotherapy, Nagoya University Graduate School of Medicine, Nagoya, [2]Department of Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, [3]Department of Medical Oncology, Mie University Hospital, Tsu, [4]Department of Breast and Endocrine Surgery, Osaka University Hospital, Osaka, [5]Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, [6]Department of Breast and Endocrine Surgery, Graduate School of Comprehensive Human Science, University of Tsukuba, Tsukuba, [7]Department of Breast Surgery, Hiroshima City Asa Hospital, Hiroshima, [8]Department of Breast and Endocrine Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, [9]Department of Surgery, Iwate Medical University, Morioka, [10]Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya and [11]Department of Biostatistics, School of Public Health, University of Tokyo, Tokyo, Japan

*For reprints and all correspondence: Masataka Sawaki, Department of Clinical Oncology and Chemotherapy, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466–8550, Japan.
E-mail: m-sawaki@med.nagoya-u.ac.jp

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Objective: This trial is conducted to investigate the benefit of trastuzumab monotherapy compared with a combination therapy of trastuzumab and chemotherapy in women over 70 years with human epidermal growth factor receptor type-2-positive primary breast cancer.
Methods: Inclusion criteria are the following: histologically diagnosed as invasive breast cancer and received curative operation for primary breast cancer; Stage I, IIA, IIB or IIIA/M0; and baseline left ventricular ejection fraction is $\geq$55%. Patients are randomized to receive either trastuzumab (8 mg/kg loading dose, 6 mg/kg every 3 weeks for 1 year) plus chemotherapy selected from regimens specified on the protocol or trastuzumab monotherapy. The primary endpoint is disease-free survival. Secondary endpoints are overall survival, relapse-free survival, safety, health-related quality of life, comprehensive geriatric assessment and cost effectiveness.
Results: Patients recruitment has been commenced in October 2009. Enrollment of 300 patients is planned during the 4-year recruitment period.
Conclusions: We hereby report the study concept.

*Key words: breast cancer – Phase III – elderly – HER2/*neu *– trastuzumab – monotherapy*

†An abstract was presented in part at 2010 Breast Cancer Symposium, Washington, DC, 1–3 October 2010.

INTRODUCTION

Trastuzumab with chemotherapy is the standard treatment as an adjuvant systemic therapy for human epidermal growth factor receptor type-2 (HER2)-positive primary breast cancer (1–4). Overexpression of HER2 has also been associated with potentially more aggressive tumors; therefore, trastuzumab is a key drug in the treatment of HER2-positive primary cancer. However, monotherapy of trastuzumab as an adjuvant treatment without concurrent or preceding chemotherapy is not conducted in clinical practice since its benefit has not been investigated as well as elderly patients (5). It has clinical significance to demonstrate the benefit of trastuzumab monotherapy without toxicity induced by chemotherapy, especially in elderly patients. Chemotherapy is not always a standard therapy in elderly patients based on the analysis of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) because of limited data (6). Careful monitoring is necessary for elderly patients due to toxicity, cardiac toxicity associated with anthracycline-containing chemotherapy (7,8), increasing in acute myeloid leukemia (AML) after adjuvant chemotherapy (9).

This trial is conducted to investigate the clinical positioning between trastuzumab monotherapy (H group) and a combination therapy of trastuzumab and chemotherapy (H + CT group) based on a randomized controlled trial in women over 70 years with HER2-positive primary breast cancer.

DIGEST OF THE STUDY PROTOCOL

Purpose

This study is conducted to investigate the clinical positioning between trastuzumab (Herceptin) monotherapy (H group) and a combination therapy of trastuzumab and chemotherapy (H + CT group) based on a randomized controlled trial in women over 70 years with HER2-positive primary breast cancer (Fig. 1). Our hypothesis includes the following two points:

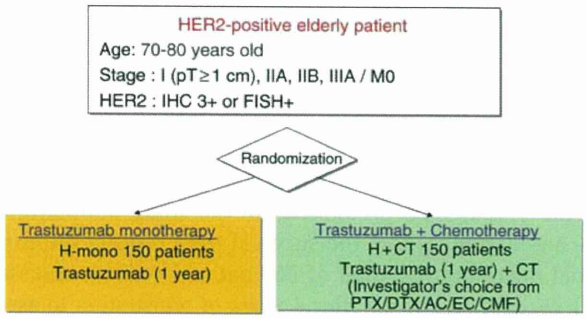

Figure 1. Study schema. Evaluation of trastuzumab without chemotherapy as a post-operative adjuvant therapy in HER2-positive elderly breast cancer patients: randomized controlled trial [RESPECT (N-SAS BC07)].
HER2, human epidermal growth factor receptor type-2; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; PTX, paclitaxel; DTX, docetaxel; AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate and 5-fluorouracil.

(i) H group is non-inferior to the H + CT group in disease-free survival (DFS).
(ii) H group is superior in safety and health-related quality of life (HRQOL).

Study Setting

This study is a multi-institutional prospective randomized controlled trial with 56 participating centers as of 31 August 2010.

Study Support

This study was funded by Comprehensive Support Project for Oncology Research (CSPOR) of Public Health Research Foundation. All decisions concerning the planning, implementation and publication of this study were made by the executive committee of this study.

Endpoints

The primary endpoint is DFS. Secondary endpoints are overall survival, relapse-free survival, adverse events, HRQOL, comprehensive geriatric assessment and cost-effectiveness analysis.

Eligibility Criteria

Inclusion Criteria

(i) Histologically diagnosed as invasive breast cancer and received curative operation for primary breast cancer.
(ii) Stage I [tumor size (pT) $\geq$1 cm), IIA, IIB or IIIA/M0; female between 70 and 80 years old.
(iii) Primary cancer is HER2-positive (either 3+ overexpression or positive by fluorescence *in situ* hybridization).
(iv) Baseline left ventricular ejection fraction is $\geq$55% measured by echocardiography or multigated acquisition scan within 4 weeks before registration.
(v) Performance status (PS) 0–1.
(vi) Sufficient organ function meeting the following criteria within 4 weeks before registration:
  (a) Leukocyte $\geq$2500 mm^3
  (b) Neutrophil $\geq$1500 mm^3
  (c) Platelet $\geq$100 000 mm^3
  (d) Serum total bilirubin $\leq$2.0$\times$ the upper limit of normal (ULN)
  (e) Alanine aminotransferase (glutamic pyruvic transaminase) or aspartate aminotransferase (glutamic oxaloacetic transaminase) $\leq$2.5$\times$ ULN
  (f) Serum creatinine $\leq$2.0$\times$ ULN
  (g) Alkaline phosphatase $\leq$2.5$\times$ ULN
(vii) No previous endocrine therapy or chemotherapy for breast cancer.
(viii) Signed written informed consent.

Exclusion Criteria

(i) Active multiple primary cancer (synchronous multiple primary cancer and invasive cancer of other organs).
(ii) Post-operative histological axillary lymph node metastasis ≥ 4.
(iii) Axillary lymph node is not histologically evaluated.
(iv) Histologically confirmed positive margin in breast conservation surgery (evaluation of margin status is based on the policy of site).
(v) History of drug-related allergy which could hinder planned treatment.
(vi) Any history or complication of the following cardiac disorders.
(vii) History of congestive heart failure, cardiac infarction.
(viii) Complication requires treatment such as ischemic cardiac disorder, arrhythmia and valvular heart disease.
(ix) Poorly controlled hypertension (e.g. systolic arterial pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg).
(x) Poorly controlled diabetes.
(xi) Continuous visit to a medial institution is considered difficult due to deterioration of activity of daily living.
(xii) Difficult to participate in the trial because of psychiatric disorder or psychiatric symptoms.
(xiii) Ineligible to the trial based on the decision of an investigator.

Patient Assignment

The CSPOR Data Center will confirm patient eligibility, and treatment will be automatically assigned according to the assignment adjustment factors for eligible patients. The following five variables will be used as assignment adjustment factors: age (70–75/76–80), PS (0/1), hormone sensitivity, lymph node metastasis and hospital.

Treatment

Combination Therapy of Trastuzumab and Chemotherapy Arm

The loading administration dose of trastuzumab is 8 mg/kg of body weight, and the maintenance dose is 6 mg/kg every 3 weeks for 1 year. Chemotherapy is selected from regimens specified on the protocol based on the decision of a physician or a patient.

(i) Paclitaxel (PTX) 80 mg/m^2 weekly administered every week for 11 cycles.
(ii) Docetaxel (DTX) 75 mg/m^2 every 3 weeks for four cycles.
(iii) Doxorubicin (A) 60 mg/m^2 and cyclophosphamide (C) 600 mg/m^2 every 3 weeks for four cycles.
(iv) Epirubicin (E) 90 mg/m^2 and cyclophosphamide (C) 600 mg/m^2 every 3 weeks for four cycles.
(v) Cyclophosphamide (C) 75–100 mg orally from days 1 to 14, methotrexate (M) 40 mg/m^2 on days 1 and 8 intravenously, and 5-fluorouracil (F) 500–600 mg/m^2 intravenously on days 1 and 8, every 4 weeks for six cycles.

Administration of trastuzumab initiates after completion of chemotherapy as a sequential combination. However, concomitant administration is allowed when combining trastuzumab with PTX, DTX and CMF.

If the hormone receptor is positive, hormone therapy is indicated. In the case of after breast conservative operation, irradiation for breast is indicated after chemotherapy.

Trastuzumab Monotherapy Arm

The loading dose of trastuzumab is 8 mg/kg of body weight, and the maintenance dose is 6 mg/kg every 3 weeks for 1 year.

If hormone receptor is positive, hormone therapy is indicated. In case of after breast conservative operation, irradiation for breast is indicated after surgery or concurrent with trastuzumab.

Stratification Factors

(i) Age at registration: 70–75/76–80
(ii) PS: 0/1
(iii) Hormone receptor status: positive/negative
(iv) Pathological nodal status: positive/negative
(v) Institution

Statistical Analysis

Main Analysis and Assessment Criteria

To evaluate the clinical position of each treatment, the estimated hazard ratio is compared with a threshold hazard ratio of 1.69. Concretely, the threshold will be used to determine whether the H + CT group is equivalent (not inferior) to the H group with regard to DFS. As an aid to interpret the trial result, we will estimate the three posterior probabilities between and outside the following two thresholds: 'the upper threshold of hazard ratio (1.69) to select the combination therapy of trastuzumab and chemotherapy' and 'the lower threshold (1.22) to select the monotherapy of trastuzumab', using the posterior distribution of log hazard ratio based on a non-informative prior.

Sample Size and Follow-up Period

The primary endpoint will require 120 events in total, given a power of 80% and a threshold hazard ratio of 1.69. Giving that the 3-year DFS probability in the study population is 68% and assuming that the survival time follows the exponential distribution, a total of 260 patients will be necessary for 3 years of follow-up after 4 years of registration to assess the 120 events. Therefore, the target number of registration was determined to be 300 since exponential distribution of survival might not be shown because of the elderly population and dropout patients were expected.

This study has been started from October 2009 and completion is scheduled in October 2016 with a registration period for 4 years and a follow-up period for 3 years.

Registration of the Protocol

The protocol was registered at the website of the University Hospital Medical Information Network (UMIN), Japan (protocol ID UMIN000002349), on 1 September 2009. Details are available at the following address: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000002854&language=E.

And also registered at ClinicalTrials.gov (protocol ID NCT01104935), on 6 November 2009. Details are available at the following address: http://clinicaltrials.gov/show/NCT01104935.

Funding

This study is supported by the Public Health Research Foundation, Japan. The corporate and individual sponsors of this study are listed on the CSPOR website (http://www.csp.or.jp/cspor/kyousan_e.html).

Conflict of interest statement

Hiroji Iwata and Yasuo Ohashi receive honoraria for speaking events from Chugai Pharmaceutical Co., Ltd.

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Lecture

解　説

がん研究企画・評価の方法論とわが国のがん研究支援体制に対する検討*

山本精一郎**　溝田友里**　吉田輝彦***

Key Words : cancer research, funding agency, grant, National Cancer Center

はじめに

がんを克服するためには効果的ながん対策を行う必要があるが，効果的ながん対策を立てる基になるのは科学的なエビデンスである．しかし，科学はニーズと関心に基づいた自由競争であるため，必ずしも網羅的にエビデンスが構築されるわけではない．限られたリソースの中で，がん克服のエビデンスを効率的に構築するためには，研究費配分を効率的に行うこと，その後の研究支援と管理，それらに対する研究者の理解と協力が必須である．これまで本邦では，がん研究の分野において，研究費配分をどのように行うことががん克服に効果的であるかという系統的な検討はあまり行われてこなかった[1)2)]．

国立がんセンターがん研究助成金による研究班18指-3(主任研究者吉田輝彦)および21特指-3(主任研究者山本精一郎)では，平成18年度より，厚生労働省系の研究費による研究に焦点をあて，がん研究の企画と評価の方法論を検討し，実証的な面から検証を行うとともに，具体的な提案を行ってきた．具体的には，厚生労働省の研究費のうち，平成21年度まで国立がんセンターが研究費配分機関(funding agency，以下FA)となっていた「がん研究助成金」「第3次対がん10か年総合戦略研究事業」「がん臨床研究事業」の3者に注目し，包括的な現状分析を行うとともに，「推進が必要な研究分野・政策的課題を系統的に把握し，支援する枠組みの作成」を試みてきた．本稿では，これまでの検討結果を紹介したい．

研究費配分に関する現状分析

平成21年度まで，がん研究助成金は国立がんセンターで行うべき研究に対する研究費を自ら研究を実施するだけでなく，FAという立場から，センター内外の研究者に配分してきた．これに対し，厚生労働科研費(第3次対がん，がん臨床の両研究事業)において国立がんセンターは基本的にはFAとしての役割が規定されているのみであり，研究者としての立場はセンター内外に区別はなかった．研究費配分のためには，米国National Institutes of Healthのように，program officer/program director(PO/PD)と呼ばれる，研究者のバックグラウンドを持った行政官(科学行政官)が専任で研究企画や運営の中心になることが望ましいが，PO/PDの役割がわが国ではあまり認識されていなかったこと，PO/PDのキャリアパスがないことなどから，上記3つの研究費については，厚生労働省や国立がんセンターの行政官が中心となり，現場の研究者の協力を得ながらFA機能を担ってきた．これら3つの研究費は，もともとの趣旨や運用が異なっていても，他者からは非常に区別のしにくい研究費となっており，研究の重複や国立がんセンターが研究者かつFAであることから利

* Strategy of funding for cancer research in Japan.

** Seiichiro YAMAMOTO, Ph.D. & Yuri MIZOTA, Ph.D.: 独立行政法人国立がん研究センターがん対策情報センター〔〒104-0045 東京都中央区築地5-1-1〕; Center for Cancer Control and Information Services, National Cancer Center, Tokyo 104-0045, JAPAN

*** Teruhiko YOSHIDA, M.D.: 独立行政法人国立がん研究センター研究所遺伝医学研究分野

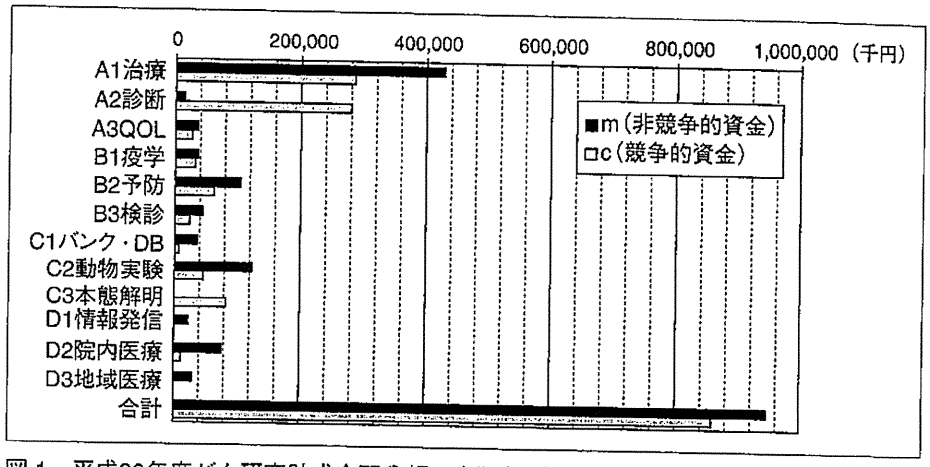

図1　平成20年度がん研究助成金配分額の内訳（研究分野別，競争的・非競争的資金別）

益相反の問題が指摘されてきた．

それに対する一つの解決策は，研究費の性格を競争的・非競争的と色分けし，がん研究助成金を国や国立がんセンターのミッションに沿った研究を行うための研究費，厚生労働科研費をより自由な研究を行うための研究費として明確に分けることである．競争的な研究費（competitive grant）とは，研究者の自由な興味・関心に基づいて実施する（curiosity-driven）研究を支援するための研究費であり，非競争的な研究費（non-competitive grant）とは，ある明確な目的を達成するための（mission-oriented）研究を支援するための研究費である．具体的にどのような研究がどちらの分類となるかについては考え方の違いがあると思われるが，一つの分類の例としては，非競争的な研究費によって支援されるべき研究には，臨床試験のインフラ整備や，大規模疫学研究の体制作り，診療ガイドライン作成やがん登録など，事業的側面のあるものが含まれ，競争的研究費によって支援されるべき研究は，これらのインフラを用いた個別の研究課題とする分け方がありうるだろう．Mission-orientedやcuriosity-drivenといった定義はmissionやcuriosityに依存するところもあるので，競争的・非競争的という区別のほうが整理しやすいかもしれない．

いずれにしろ，平成20年度までは，このような分類を明示的に行ってこなかったため，がん研究助成金，厚労科研費のどちらもが競争的・非競争的研究費の色合いを持ち，支援している研究の中身から研究費の性格の違いを判断することが難しかった．図1および図2は，これら3つの研究費によって支援されている研究を，後述する研究分野ごとにわれわれが競争的（competitive）/非競争的（mission-oriented）に分けたものである．一つの研究の中に複数の研究があること，報告書や発表会だけでは研究の中身をすべて判断するのが難しいことなどから，研究班を1単位とし，研究班の課題名から分類を行った．課題名から分類を行うことには限界があるものの，がん研究助成金，厚労科研費の両方に競争的・非競争的研究が混在していることは明らかであり，その割合は研究分野によって異なることもわかる．このように混在していた理由として，厚労科研費が文部科学省の科研費に比べ，もともと応用や実践を施行した研究を対象とするというデマケ（demarcation）があり，その意味で具体的なテーマを募集する形のmission-orientedな性格の研究費であったこと，がん研究助成金ががん研究の基盤を支えるという意味で，文科省的なcuriosity-drivenの研究を支援することも視野に入れていたことなども性格の違いを区別するのが難しかったことの理由として挙げられるであろう．これらは必ずしも悪いわけではないが，支援する分野の偏りや漏れといった問題点や重複による非効率性につながっていたことは否定できない．

研究の採択と評価の方法に関する現状分析

これらの厚生労働省系の研究費に対して指摘されてきたもう一つの問題点として，研究結果の評