Estrogen Receptor Positive and Progesterone Receptor Negative Breast Cancer: the Role of Hormone Therapy

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Received: 14 February 2020 / Accepted: 1 June 2020 / Published online: 9 June 2020
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Abstract

ER+/PR− (estrogen receptor positive and progesterone receptor negative) tumors constitute only a small portion of the breast cancer population. Patients with ER+/PR− tumors, however, are characterized by worse survival compared to patients with ER+/PR+ (estrogen receptor positive and progesterone receptor positive) tumors. Controversy exists regarding the efficacy of hormone blocking therapy for patients with ER+/PR− tumors. The NCDB was queried between 2004 and 2015, and patients with invasive ER+/PR− tumors were identified. We employed univariate Cox proportional hazards to compare outcomes among patients that did or did not receive hormone blocking therapy. We identified 138,398 patients with invasive ER+/PR− tumors, 32,044 (23%) of whom did not receive hormone blocking therapy. The reasons for not receiving hormone blocking therapy included contraindications to treatment, death, patient refusal, and unknown. There were no significant differences in race, income quartile, or education quartile between patients who did and did not receive hormone blocking therapy. Patients who did not receive hormone blocking therapy underwent surgical assessment of the axilla more frequently than those who did receive hormone therapy. Our analysis demonstrated that hormone blocking therapy administration was associated with increased overall survival for up to 10 years of follow up (HR: 0.58; 95% CI: 0.56–0.59, $p < 0.001$). Hormone blocking therapy may be associated with increased survival for breast cancer patients with ER+/PR− tumors. Although this benefit may last for years after completion of the course, up to 25% of patients do not receive this treatment. Strategies to increase the utilization and adherence to hormone blocking therapy regimens may improve patient survival outcomes.

Keywords Breast cancer · Hormone therapy · ER+/− · PR+/−

Introduction

Among American women, breast cancer is the most common cancer, corresponding to 30% of all cancers, and is the second largest cause of cancer mortality (15%) [1]. Currently, research initiatives are focused on the heterogeneity of individual tumors and the role of their distinct histological and clinicopathologic characteristics for the design of personalized treatment plans. Among these characteristics, steroid hormone receptor status has been shown to reliably predict overall outcomes [2–14]. For this reason, the American Joint Commission of Cancer

formally included hormone status in the updated breast cancer staging system [15]. ER+/PR+ is the most common variant of breast tumors, while ER+/PR− cases represent approximately only 1.5–3.4% of patients; this cohort tends to have worse survival outcomes than the former group [2, 8, 16–19].

Targeted hormone receptor therapies, such as Tamoxifen (TAM) and aromatase inhibitors, are well documented to improve the outcomes in breast cancer patients with ER+/PR+ disease [20]; [21]. The presence of hormone blocking therapy resistance, however, is one of the potential factors that may be responsible for the observed survival difference between ER+/PR+ and ER+/PR− patients [2, 18]. Previous studies have demonstrated that ER+/PR− patients are less likely to respond to hormone blocking therapy in the metastatic setting [22]. This relationship, however, does not appear to be as significant for patients with early stage disease [23, 24].

While the physiology and extent of the resistance have not been well defined, a possible association with the expression of HER2 proteins has been suggested. [2]. In this context, researchers and clinicians are split regarding the efficacy of

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hormone blocking therapy for patients with ER+/PR– cancers [25]. The purpose of our study is to better understand the impact of hormone blocking therapy on the overall and progression-free survival of ER+/PR– breast cancer patients. Furthermore, our study will seek to identify groups of patients where hormone blocking therapy is underutilized.

Methods

Patient Demographics

Eligible patients treated for breast cancer in the USA between 2004 and 2015 were identified from the National Cancer Database (NCDB) registry. Patients with both ER+/PR+ and ER+/PR– cancers were queried and divided into two categories based on receipt of hormone blocking therapy. We also examined the following variables: age, race, charlson score, insurance carrier, income quartile, education quartile, community residence (urban/rural), patient residence category, type of hospital where they were treated, T stage (0–IV), presence or absence of axillary staging with sentinel lymph node biopsy or axillary lymph node dissection (lymphadenectomy), and margin status. Age over/under 50 years old was used as a proxy for menopausal status, although HER2 status data were only available from 2010 to 2015.

Statistical Analysis

Demographic and clinical characteristics of women who received hormone blocking therapy were compared to those that did not receive hormone blocking therapy using Chi squared and Student *t* tests with unequal variances for categorical and continuous variables, respectively. Kaplan–Meier plots were produced and described the probability of overall or progression-free survival by receipt of hormone blocking therapy; log-rank tests were used to compare treated and untreated groups.

Unadjusted and multivariable Cox proportional hazards regression was used to evaluate the association of hormone blocking therapy status with progression-free and overall survival. Adjusted models included age, race, T stage, N stage, receipt of chemotherapy, and receipt of radiation. Individuals entered risk sets at the date of diagnosis and were followed until death or date of cancer recurrence. Individuals who did not experience these outcomes were recorded at their last clinical visit (for overall survival). Proportional hazard assumptions were evaluated through visual inspection of the log–log survival curves vs. (log) time and scaled Schoenfeld residual plots over time for each variable. Results of regression models are presented as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). A $p < 0.001$ was considered

statistically significant. All analyses were performed using STATA Version 14.1 (StataCorp, College Station, TX).

Results

We identified 138,398 female patients with ER+/PR– invasive breast cancer from the registry records of the National Cancer Database (NCDB) between 2004 and 2015. The median time to initiation of hormone blocking therapy was 169 days with IQR (91–249). Patients who did not receive hormone blocking therapy underwent lymphadenectomy more frequently than those who did receive hormone blocking therapy ($p < 0.001$). There were no significant differences in race, income quartile, or education quartile between patients who did and did not receive hormone blocking therapy (Table 1).

We identified 871,857 female patients with ER+/PR+ invasive breast cancer from the registry records of the NCDB between 2004 and 2015. The median time to initiation of hormone blocking therapy was 158 days with IQR (80–221). There were no significant differences in race, income quartile, or educational quartile between patients who did and did not receive hormone therapy.

About 106,354 (76.9%) patients from the ER+/PR– population received hormone blocking therapy, while 32,044 (23.2%) did not. About 718,351 (82.39%) patients from the ER+/PR+ population received hormone blocking therapy while 153,506 (17.61%) did not. There was a significant difference between receipts of hormone blocking therapy ($p < 0.001$). Of the ER+/PR– patients that did not receive hormone therapy, 1993 (1.4%) patients had contraindications to receiving hormone blocking therapy, 1553 (1.1%) patients were prescribed hormone blocking therapy but it was never administered, 5710 (4.1%) patients refused to receive hormone blocking therapy, and 22,579 (16.3%) patients were not offered hormone blocking therapy for unknown reasons. Two hundred nine patients (0.2%) died before administration of hormone blocking therapy and were not included in analysis.

Of the 134,510 ER+/PR– patients, receipt of hormone blocking therapy varied by cancer stage. Stage I (75.24%), stage II (80.42%), and stage III (80.13%) patients received hormone blocking therapy at a significantly ($p < 0.001$) higher rate than stage IV (65.12%) patients. Our unadjusted analysis revealed that ER+/PR– patients who received hormone blocking therapy had a statistically significant improved 10-year overall survival compared to those who did not receive hormone blocking therapy (HR: 0.59; 95% CI: 0.57–0.61, $p < 0.001$) (Fig. 1). Upon adjustment for cancer stage, receipt of hormone blocking therapy was more strongly associated with improved overall survival (HR: 0.53; 95% CI: 0.52–0.55) (Table 2). Although the benefit of hormone blocking therapy was not as strong in stage IV patients (HR: 0.73)

Table 1 Clinicopathologic characteristics stratified by use of hormone therapy

Characteristic	No hormone therapy		Hormone therapy		P value	Total	
	N	%	N	%		N	%
Total	32,044	23.2	106,354	76.9	N/A	138,398	100.0
Age, years, median (IQR)	63 (53–75)		61 (53–70)		< 0.001	61 (53–71)	
Charlson score					< 0.001		
0	27,059	84.4	90,294	84.9		117,353	84.8
1	4041	12.5	13,269	12.5		17,283	12.5
≥ 2	971	3.0	2791	2.6		3762	2.7
Insurance status					< 0.001		
Private	15,190	48.4	56,856	54.2		72,046	52.9
Medicare	1823	5.8	6481	6.2		8304	6.1
Medicaid	13,404	42.7	38,423	36.6		51,827	38.0
Other/Unknown	962	3.1	3103	3.0		4065	3.0
Income quartile					< 0.001		
Q1	3267	10.3	9791	9.3		13,058	9.5
Q2	5116	16.2	16,775	15.9		21,891	15.9
Q3	8608	27.2	29,225	27.7		37,833	27.6
Q4	14,677	46.4	49,832	47.2		64,509	47.0
Education quartile					< 0.001		
Q1	4044	12.8	12,075	11.4		16,119	11.7
Q2	6676	21.1	21,713	20.6		28,389	20.7
Q3	7828	24.7	27,011	25.6		34,839	25.4
Q4	13,129	41.5	44,854	42.5		57,983	42.2
Tumor stage					< 0.001		
Stage I	16,713	55.2	50,796	48.7		67,509	50.2
Stage II	9136	30.2	37,528	36.0		46,664	34.7
Stage III	3515	11.6	14,176	13.6		17,691	13.2
Stage IV	923	3.1	1723	1.7		2646	2.0
Lymphadenectomy					< 0.001		
No	3364	10.6	3865	3.6		7229	5.3
Yes	28,426	89.4	102,171	96.4		130,597	94.8

N/A not available

compared to stages I–III (HR: 0.50–0.53), receipt of hormone blocking therapy was still significantly associated with improved patient outcomes.

For patients with ER+/PR– cancers, there was no significant difference in receipt of hormone blocking therapy in premenopausal patients (76.30%) compared to postmenopausal patients (76.96%) ($p < 0.03$). In ER+/PR+ patients, however, 84.40% of premenopausal patients received hormone blocking therapy compared to 81.77% of postmenopausal patients ($p < 0.001$).

About 69,014 ER+/PR– patients reported HER2 status from 2010 to 2015. About 51,652 patients (74.84%) were HER2–, while 16,128 patients (23.37%) were HER2+, and 1604 patients (2.32%) were borderline/indeterminant. HER2+ patients had statistically significant survival compared to HER2– patients (HR: 0.79; 95% CI: 0.74–.84,

$p < 0.001$). Borderline patients did not demonstrate a significant difference in survival (HR: 1.10; 95% CI: 0.94–1.29, $p = 0.214$).

Discussion

Breast cancer is a heterogeneous disease with varying clinicopathologic characteristics. Estrogen receptors are expressed in two-thirds of breast cancers but only a subset of ER+ tumors are also PR– [26]. Hormone positive breast cancer includes a heterogeneous group of malignant cells with varying degrees of receptor representation. The breast gland undergoes several prominent phases during adult life with significant functional, structural, and morphological growth, which is mediated through a complex hormonal mechanism [27]. The interplay

Fig. 1 Kaplan–Meier survival curves by receipt of hormone therapy. $p < 0.001$

P value: <0.001

Table 2 Unadjusted and adjusted Cox proportional hazards regression evaluating the association of selected patient demographic, clinical characteristics, and receipt of hormone therapy and risk of death and progression-free survival in women with ER+/PR– breast cancer, treated between 2003 and 2017 and registered in NCDB

Characteristic	Univariable				Multivariable			
	Hazard ratio	95% CI		P value	Hazard ratio	95% CI		P value
Hormone therapy								
No hormone therapy	Reference	—	—	—	Reference	—	—	—
Hormone therapy	0.58	0.56	0.59	< 0.001	0.59	0.57	0.60	< 0.001
Age, years	1.05	1.05	1.05	< 0.001	1.06	1.05	1.06	< 0.001
Patient race								
White	Reference	—	—	—	Reference	—	—	—
Black	1.20	1.15	1.25	< 0.001	1.25	1.19	1.30	< 0.001
Other/Unknown	0.65	0.60	0.71	< 0.001	0.79	0.73	0.87	< 0.001
Charlson score								
0	Reference	—	—	—	Reference	—	—	—
1	1.77	1.71	1.83	< 0.001	1.42	1.37	1.47	< 0.001
≥ 2	3.55	3.36	3.75	< 0.001	2.44	2.30	2.59	< 0.001
Insurance status								
Private	Reference	—	—	—	—	—	—	—
Medicare	2.08	1.97	2.20	< 0.001	—	—	—	—
Medicaid	2.77	2.96	2.85	< 0.001	—	—	—	—
Other/Unknown	1.76	1.62	1.90	< 0.001	—	—	—	—
Income quartile								
Q1	Reference	—	—	—	—	—	—	—
Q2	0.93	0.89	0.98	0.004	—	—	—	—
Q3	0.86	0.82	0.90	< 0.001	—	—	—	—
Q4	0.67	0.64	0.70	< 0.001	—	—	—	—

Table 2 (continued)

Characteristic	Univariable				Multivariable			
	Hazard ratio	95% CI		P value	Hazard ratio	95% CI		P value
Education quartile								
Q1	Reference	–	–	–	–	–	–	–
Q2	0.97	0.92	1.01	–	–	–	–	–
Q3	0.91	0.88	0.96	< 0.001	–	–	–	–
Q4	0.72	0.69	0.75	< 0.001	–	–	–	–
Geographic setting								
Metropolitan	Reference	–	–	–	–	–	–	–
Urban	1.10	1.06	1.14	< 0.001	–	–	–	–
Rural	1.16	1.06	1.28	0.001	–	–	–	–
Type of hospital								
Community	Reference	–	–	–	Reference	–	–	–
Academic/integrated network	0.82	0.81	0.85	< 0.001	0.92	0.89	0.95	< 0.001
Tumor stage								
Stage I	Reference	–	–	–	Reference	–	–	–
Stage II	1.80	1.74	1.86	< 0.001	2.03	1.96	2.10	< 0.001
Stage III	4.03	3.90	4.18	< 0.001	4.87	4.69	5.05	< 0.001
Stage IV	11.54	10.93	12.18	< 0.001	12.97	12.22	13.76	< 0.001
Metastatic disease at diagnosis								
No	Reference	–	–	–	–	–	–	–
Yes	6.95	6.64	7.28	< 0.001	–	–	–	–
Lymphadenectomy								
No	Reference	–	–	–	–	–	–	–
Yes	0.31	0.30	0.32	< 0.001	–	–	–	–
Margin status								
Negative	Reference	–	–	–	Reference	–	–	–
Positive	2.08	1.99	2.17	< 0.001	1.37	1.31	1.44	< 0.001

and mechanism of action of estrogen, progesterone, and estradiol hormones on breast tissue and breast cancer cells remains elusive. Both hormone deprivation and hormone excess have been associated with cancer cell control and point to the complex mechanism by which the cancer cell growth is modulated [28]. Selective estrogen receptor modulators (SERMs), like Tamoxifen, are standard treatment for hormone receptor positive breast cancer and block the effects of estrogen in breast tissue. The recommended duration of therapy for SERMs is 5 years with a lasting effect up to 20 years [29–33]. For postmenopausal women, aromatase inhibitors like anastrozole are prescribed to block estrogen production, while exemestane is prescribed for women with a history of tamoxifen treatment [34, 35].

In our study population there was a difference in receipt of hormone blocking therapy between ER+ patients with PR+ type (82.39%) and PR– type (76.85%) cancers. Differences in receipt of hormone blocking therapy based on PR receptor status could be attributed to literature describing the reduced effectiveness of hormone blocking therapy in ER+/PR–

tumors. A recent study demonstrated a 77% hormone blocking therapy response rate for ER+/PR+ breast cancers, while ER+/PR– tumors had a response rate of only 27% [36]. Furthermore, some studies have shown that 30–40% of patients with ER+/PR– cancers do not respond to targeted hormone blocking therapies [37]. Nonetheless, our study found an improved overall survival in patients with ER+/PR– tumors who received hormone blocking therapy (HR: 0.59). Hormone blocking therapy appears underutilized as 22,579 (16.3%) of ER+/PR– patients did not receive hormone blocking therapy for unknown reasons.

Previous studies have described a lack of responsiveness to hormone blocking therapy for ER+/PR– tumors in the metastatic setting but little difference in patients with early stage disease. Our study, however, suggests that hormone blocking therapy is effective in patients with stage IV ER+/PR– cancer. Although patients with stage IV disease had a lesser degree of improvement in survival outcomes compared to stages I–III, receipt of hormone blocking therapy was still associated with improvement in survival for patients with stage IV disease

(HR: 0.73) Of note, just 65.12% of patients with stage IV ER+/PR– disease received hormone blocking therapy compared to patients with stage I (75.24%), II (80.42%), and III (80.13%) disease. Since hormone blocking therapy may be associated with improved 10-year survival outcomes in late stage ER+/PR– breast cancer patients, stage IV patients should be considered to receive hormone blocking therapy.

Despite demonstrating clinically relevant survival outcomes, this study has several limitations. The demonstrated improved survival in stage IV patients with ER+ disease may be due to hormone blocking therapy given in combination with CDK4/6 inhibitors in recent years. Despite a statistically significant difference in receipt of hormone therapy between ER+/PR– patients and ER+/PR+ patients, a high percentage (17%) did not receive hormone blocking therapy. The study's retrospective nature prevents insight into the clinical rationale behind the decision to administer or refrain from hormone blocking therapy treatment. Although HER2 protein status can greatly influence treatment plans, this measure was added to the NCDB in 2010 and was limited for this study. Lastly, the NCDB does not report the type of hormone blocking therapy administered, which limits the ability to determine individual drug efficacies and compliance rates.

Conclusion

Our study is one of the first to compare outcomes of ER+/PR– disease based on the receipt of hormone blocking therapy. The results suggest that hormone blocking therapy may be associated with improved overall and progression-free survival with up to 10 years of follow up. Hormone blocking therapy may be underutilized; however, as nearly 25% of patients do not receive it. Investigation into the root cause of this underutilization, in conjunction with patient and provider education, could lead to improvement in outcomes for patients with ER+/PR– breast cancer.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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