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ORIGINAL ARTICLE

The effect of renin-angiotensin-system inhibition on survival and recurrence of N3+ breast cancer patients

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Summary

Purpose: *The purpose of this study was to evaluate the association between the rennin-angiotensin system (RAS) inhibition and the risk of breast cancer (BC) recurrence and progression in N3 positive patients.*

Methods: *The medical records of patients treated for N3 positive BC in Hacettepe Cancer Institute between 2005 and 2012 were evaluated. Angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) users were defined as patients who took these medications for at least 6 months in no evidence of disease (NED) stage after the initial diagnosis. The primary and secondary outcome was disease-free survival (DFS) and overall survival (OS). Kaplan–Meier and Cox proportional hazard models were used.*

Results: *A total of 218 pathologic N3 BC patients were included. Follow up ranged from 12 to 212 months (median 49.58). Thirty one patients used ACE inhibitors/ARBs. Univariate analysis showed BC recurrence was lower and OS was higher among patients who used ACE inhibitors/ARBs, however without reaching statistical significance (p=0.38 and p=0.24, respectively). RAS inhibition was associated with reduced risk of pathologic N3 BC recurrence.*

Conclusion: *To the best of our knowledge this is the second study showing that the use of ACE inhibitors/ARBs may be effective in N3 BC. Because of the limited therapeutic options in BC, new drugs or new therapeutic modalities should be considered. In the future, studies with long-term follow-up may be helpful for their implication in clinical practice.*

Key words: *breast cancer, N3 positive, RAS inhibition, recurrence, survival*

Introduction

BC is a leading cause of cancer-related morbidity and mortality among women worldwide. Moreover, after primary therapy a significant proportion of patients will eventually develop recurrent disease despite the use of modern adjuvant treatments. Differentiating patients into those with high and low risk of recurrence is currently based on clinical and pathologic factors including age, menopausal status, hormone receptors, HER-2 expression, histological grade, tumor size and lymph node involvement [1,2]. Among these factors, nodal status is still considered as one of the most important prognostic factors in BC management. Patients with 10 or more positive axillary lymph nodes are classified into pathologic N3 (pN3) stage and comprise the worst prognostic group next to stage IV. According to the latest reports, the outcome of pN3 disease has improved over the past two decades with the use of effective systemic adjuvant treatment, with 5-year DFS and OS rates of 66% and 81%, respectively [3,4]. Although the survival rates of patients with pN3 disease have increased, the prognosis is still poor and the risk for both local and systemic recurrence is currently high. This situation urges for a continuous search of new treatments to decrease the risk of recurrence and progression in pN3 BC patients.

Currently, several non-chemotherapeutic drugs including non-steroidal anti-inflammatory

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drugs (NSAIDs), ACE inhibitors, ARBs and statins have shown evidence of anti-neoplastic effect *in vitro*, *in vivo*, and even clinically [5-8]. In addition, epidemiologic studies have found that patients on ACE inhibitors and ARBs had lower risk of developing cancer or cancer recurrence [9,10].

RAS is traditionally considered an endocrine system regulating blood pressure and body fluid homeostasis. Angiotensin II is the physiologically active mediator of RAS. The biological roles of angiotensin II are mediated by high-affinity membrane-bound receptors, which are classified into two subtypes: angiotensin II type 1 receptor (AT1R) and angiotensin II type 2 receptor (AT2R) [11]. Angiotensin II receptors have been found on the cell surface and cytoplasm of human tumors such as BC, hepatic carcinoma, renal carcinoma, colorectal carcinoma, squamous cell carcinoma and sarcomas [12-17]. Blockade of the RAS downregulates several key features which are connected to cancer development, such as proliferation, migration, angiogenesis, tumor growth and metastasis [18,19]. In a retrospective study from Houston, Chae et al. showed that the use of ACE inhibitors/ARBs, statins and the combination of both were all associated with a reduced risk of BC recurrence [20].

BC recurrence in pN3 patients is associated with significant morbidity, reduced quality of life and poor prognosis. Recent studies demonstrate that ACE inhibitors or ARB administration were able to reverse angiotensin II-induced angiogenesis, anti-inflammatory and anti-apoptosis through AT1 receptor. Based on this evidence, we hypothesized that patients with pN3 disease might benefit from the use of these two types of drugs. Our study is the second to suggest an individual as well as additive potential role of ACE inhibitors or ARBs as chemopreventive agents for patients with a history of pN3 BC.

Methods

A group of 218 N3 BC patients diagnosed and treated at Hacettepe University Hospital between 2003 and 2012 with no distant metastases at the time of diagnosis were enrolled into this study. Patients were categorised into two groups according to their treatment regimens with RAS inhibition (ACE inhibitors and ARBs) due to the presence of hypertension, heart failure, or coronary arterial disease. Due to potential effect on OS and DFS survival, patients with metastatic disease were excluded from the study. Relatively small sized N3b and N3c patients were also excluded from the study. Patients with RAS inhibition and receiving additional therapeutic modalities like statins, aspirin and other NSAIDs were also excluded from the study.

ACE inhibitors or ARBs users were described as patients who took the medications in NED stage for at least 6 months. NED condition included patients who were taking the medications when they were diagnosed and patients who started taking these drugs after the diagnosis but before any recurrence was evident.

The primary outcome of this study was DFS, including the time lapse from diagnosis to the first recurrence (local, systemic, or death due to BC). The secondary outcome was OS. The following variables were recorded from ACE inhibitors or ARB users and non-users: age, menopausal status, HER-2 status, estrogen and progesterone receptor status, clinical stage, tumor size, number of lymph nodes, and treatment received (surgery, radiation therapy, chemotherapy, hormone therapy). Both groups were evaluated in terms of clinical and pathologic features, treatment regimens, the effect of RAS inhibition on local and distant recurrence and survival.

Statistics

OS was measured from the date of diagnosis to the date of death from any cause. DFS was measured from the date of first definitive treatment to the date of first relapse or death from any cause. The Kaplan–Meier model and log rank test were used to test survival differences between the groups. Bivariate analyses were performed to compare baseline characteristics using x^2 test and Student's t-test. Sequential Cox proportional hazards regression model was used to adjust for potential confounders and to check for interactions. A p value <0.05 was considered statistically significant.

Results

The mean age of the whole group of 218 N3 BC patients was 49.7±12.0 years. The median period of follow-up was 49.58 months (range 12-212) and follow-up was completed in approximately 80% of the patients. Patients were randomly grouped according to RAS inhibition; 31 patients had RAS inhibition (group 1), and 187 patients had not RAS inhibition (group 2). The median patient age was 61 years (range 45-92) in group 1 and 46 years (range 21-78) in group 2 ($p<0.001$). No statistically significant difference was observed concerning tumor stage, grade, tumor histology, lymphatic and/or vascular invasion (LVI), perineural space invasion (PNI) and extracapsular extension (ECE) between the two groups. Table 1 summarizes the baseline characteristics of the study population. In both groups most of the patients had grade 2/3, T2/T3 sized tumors with invasive ductal histology. Median tumor size for group 1 was 4.83 cm (range 0.4-17), and 4.37 (range 1.30-12) for group

Table 1. Tumor characteristics

Characteristics	*Group 1 RAS inhib (+) N (%)*	*Group 2 RAS inhib (-) N (%)*	*p value*
N	31	187	
Median age, years (range)	61 (45-92)	46 (21-78)	<0.001
Tumor size			
I	2 (6.5)	20 (10.7)	
II	16 (51.6)	81 (43.3)	
III	12 (38.7)	71 (38)	0.765
IV	1 (3.2)	12 (6.4)	
Unknown	0 (0)	3 (1.6)	
Median tumor size, cm (range)	4.8 (0.4-17)	4.3 (1.3-12)	0.858
Median number of positive lymph nodes (range)	18.4 (10-39)	17.8 (10-64)	0.652
Grade			
I	3 (9.7)	12 (6.4)	
II	13 (41.9)	68 (36.3)	
III	12 (38.7)	92 (49.2)	0.534
Unknown	3 (9.7)	5 (2.6)	
Histology			
Ductal	25 (80.6)	154 (82.4)	
Lobular	1 (3.2)	14 (7.5)	
Mixed	4 (12.9)	15 (8.0)	0.665
Other	1 (3.2)	4 (2.4)	
ER			
Positive	21 (67.7)	112 (61.2)	0.488
Negative	10 (32.3)	71 (38.8)	
PR			
Positive	17 (54.8)	104 (57.5)	
Negative	14 (45.2)	77 (42.5)	0.785
cerbB2			
Positive	10 (32.3)	77 (41.2)	0.348
Negative	21 (67.7)	110 (58.8)	

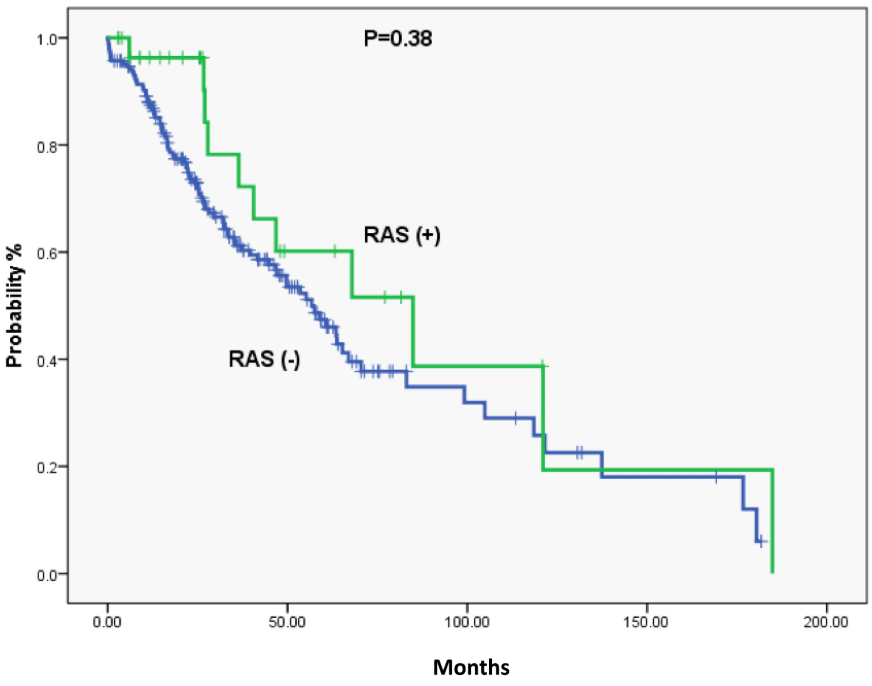

Figure 1. Disease free survival.

Table 2. Treatment modalities

Modalities	*Group 1 RAS inhib (+) N (%)*	*Group 2 RAS inhib (-) N (%)*	*p value*
Surgery			
Modified radical mastectomy	29 (93.5)	163 (88.6)	0.688
Lumpectomy	2 (6.5)	23 (11.4	
Adjuvant chemotherapy			
Anthracycline	14 (38.7)	73 (39)	0.45
Taxane	3 (9.79)	6 (3.2)	0.023
Anthracycline+taxane	12 (45.1)	107 (57.2)	0.015
None	2 (6.5)	1 (0.6)	0.001
Radiotherapy			
Yes	29 (93.5)	181(97.3)	0.272
No	2 (6.5)	5 (2.7)	
Hormone therapy			
Tamoxifen	4 (12.9)	88 (47.1)	<0.001
Aromatase inhibitor	19 (61.3)	42 (22.5)	<0.001
None	8 (25.8)	57 (30.3)	0.35
Trastuzumab	7 (22.6% of HER2+)	51 (27.3% of HER2+)	0.584

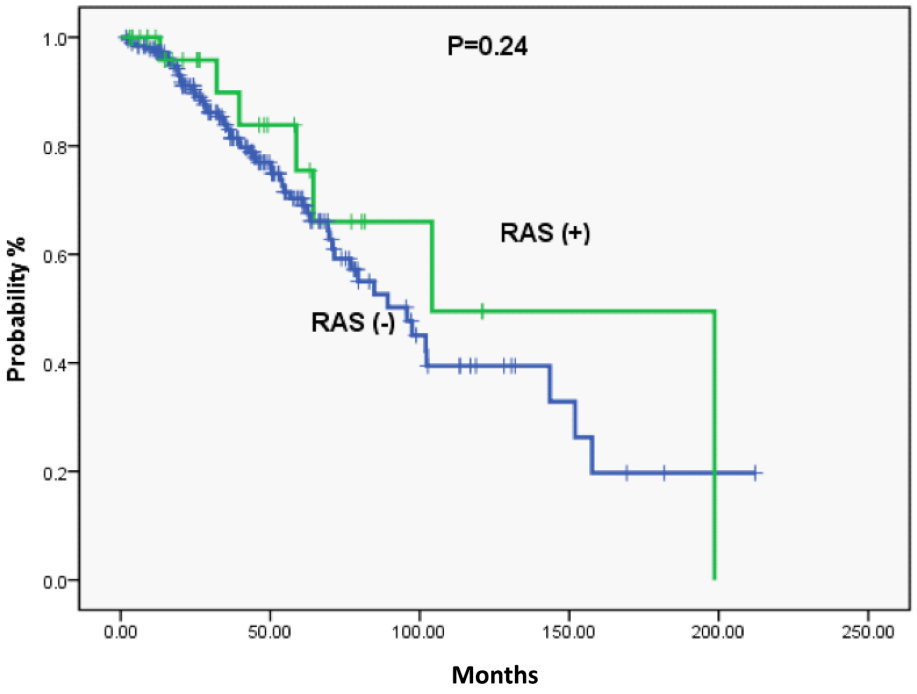

Figure 2. Overall survival.

2 (p=0.858). There was no statistically significant difference between the groups in terms of median number of positive lymph nodes (group 1: 18.48/range 10-39; group 2: 17.84/range 10-64, p=0.652).

Most of the patients (28;90.5%) with RAS inhibition were post-menopausal. The groups were very similar in terms of ER, PR and HER2 expression (Table 2). All of the patients receiving RAS inhibition had adjuvant therapy. Of the patients not receiving RAS inhibition 18 (8.3%) had neo-adjuvant therapy and 169 (90.4%) had adjuvant treatment. After a median follow up of 49.58 months (range 12-212) 7 patients in group 1 and 57 in group 2 died (p=0.371). Eleven patients in group 1 and 90 in group 2 (p=0.248) developed recurrence of BC. Five-year OS and DFS in group 1 was 60.2 % and 75.5% respectively and 50.1 % and 69.0% in group 2 (p=0.24 and p=0.38, respectively) (Figures 1 and 2).

Discussion

Despite the fact that the findings did not reach statistical significance, the disease recurrence rate of pN3 BC patients receiving RAS inhibitors was relatively lower, and DFS and OS were higher. To our knowledge, this is the second study showing that RAS inhibitors reduce BC recurrence and progression in pN3 patients. BC recurrence and progression in pN3 patients is associated with significant morbidity, reduced quality of life and poor prognosis [21]. Today, implementation of endocrine treatments and molecular based therapeutics with effective chemotherapeutic agents have contributed to rapid improvement in DFS and OS. Despite these developments there is a need for new treatment modalities in pN3 BC patients.

RAS inhibitors are widely used as antihypertensive drugs, and the reports of organ protective effects by ACE inhibitors and ARBs are increasing, including inhibition of cardiac hypertrophy, diabetic nephropathy, and diabetic retinopathy [22]. With respect to anticancer effects, Lever et al. [23] reported that the long-term use of ACE inhibitors reduced the incidence of cancer in a prospective cohort study, though they did not explore the underlying mechanisms. Since then, in addition to cardiovascular homeostasis by RAS, increasing evidence indicates a role of RAS components expressed in various cancer sites which are involved in cancer progression by regulating cell proliferation, angiogenesis, inflammation and tissue remodelling [18,19]. On the other hand, a meta-analysis denied the reduced cancer incidence with ACE inhibitors [24] and increased risk of cancer incidence was also reported with ARBs [25].

In an *in vivo* model, angiotensin I-induced angiogenesis, anti-inflammatory and anti-apoptosis through AT1 receptor, which involved activation of vascular endothelial growth factor, NF kappa β, apoptosis pathway, and ARBs administration were able to reverse all the above effects [26]. Concerning BC, there is evidence for an association between angiotensin II and BC risk. AT1R has been described to be overexpressed in 10–20% of BC cases [27]. As in other tissues, angiotensin II acts on the AT1R to promote cell proliferation in BC cells [12]. Moreover, it is demonstrated that angiotensin II increases the expression of angiogenesis-related genes [28]. The ACE gene, located on chromosome 17q23, may contain many polymorphisms. Furthermore, several studies have explored the association between the polymorphisms of RAS gene and BC risk; however, the conclusions were inconsistent. Koh et al. [29] conducted a polymorphism analysis in angiotensin II type 1 receptor and angiotensin I converting enzyme genes among Chinese women, which revealed the benefit of ACE inhibitors to reduce the risk of BC compared with non-ACE inhibitors users. Also, Koch et al. in another study [30] showed that women carrying the low-activity (A and I) alleles of the ACE A-240T and I/D polymorphisms would have lower ACE levels and decreased synthesis of angiotensin II and, consequently, would be less susceptible to developing BC.

Another study by Haiman et al. assessed the relationship between A-240T and I/D ACE variants and BC risk in a case-control analysis of African-American, Japanese, Latinos and white women in the Multiethnic Cohort study [31]. In this study carriers of A or I alleles of the A-240T and I/D ACE polymorphisms had not decreased risk of BC. However, the authors observed a modest positive association between the I/I ACE genotype and BC risk.

Except preventive and genetic studies, there are certain studies investigating the potential relationship between RAS inhibition and recurrence of pN3 BC patients. In a recent retrospective study entitled "reduced risk of breast cancer recurrence in patients using ACE inhibitors, ARBs, and/or statins" conducted by Chae et al. [20], the authors found that patients who used ACE inhibitors or ARBs or statins had significantly lower incidence of BC recurrence, with the greatest reduction noted for patients who used both groups of drugs. In this study a total of 168 patients used ACE inhibitors or ARBs for at least 6 months. Fifteen percent (25/168) of the ACE inhibitors or ARBs users recurred compared with 23% (124/534) of non-users (OR=0.58, 95% CI:0.36–0.92; p=0.023). The Kaplan–Meier survival analysis revealed that ACE inhibitors or ARB users had a significant DFS benefit compared with non-users (median survival 55.0 vs 50.0 months, respectively; log-rank test, p=0.012). However, no benefit was found in OS (median OS 55.5 vs 55.0 months; log rank test, p=0.47). In this study patients who used statins had an approximately 56% reduction in their risk of recurrence, but those who also consumed ACE inhibitors or ARBs had an additional 40% reduction in that risk. This additive effect may be explained by the fact that both drugs have different molecular mechanism of action. This study is the first to suggest an individual as well as an additive potential role of statins and ACE inhibitors or ARBs as chemopreventive agents for patients with a history of stage II or III BC.

Following the publication of studies related to recurrence in BC with RAS inhibitors usage, we investigated the role of RAS inhibitors on recurrence, DFS and OS in N3 BC patients. In our study population, while 11 of 31 patients with RAS inhibition had disease recurrence, 90 of 187 without RAS inhibition developed recurrence (p=0.248). The DFS and OS were relatively higher in patients taking RAS inhibition but the difference was not significant. The groups were similar in terms of tumor characteristics and treatment modalities. Most of the patients with RAS inhibition were postmenopausal and had comorbid diseases. Absence of significance concerning the OS may be related to this reason. Owing to its high risk for recurrence, poor prognosis and increased angiogenesis - especially in N3 BC - we aimed to observe the effect of RAS inhibition on these patients. Due to its potential effect on OS and DFS, patients with metastatic disease were excluded from the study. Most of the patients in group 1 were receiving ARBs and ACE inhibitors and none of the patients had ARBs and ACE inhibitors combination.

This study has a few limitations. First, it was retrospective, but the study groups were almost homogeneous except age and adjuvant therapy options. Second, our study population was smaller compared to other studies and the RAS inhibition group had increased comorbidities (heart failure, coronary artery disease). The last limitation was the lack of polymorphism analysis in angiotensis II type 1 receptor and angiotensin I converting enzyme genes A-240T and I/D ACE polymorphisms.

In conclusion, RAS inhibition in pN3 BC patients may reduce the ratio of recurrence and mortality. Non-chemotherapeutic drugs, like RAS inhibitors, may improve the effectiveness of chemotherapy in BC patients and this possibility needs to be investigated with further studies with larger patient numbers.

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