RESEARCH ARTICLE

Significance of ABO-Rh Blood Groups in Response and Prognosis in Breast Cancer Patients Treated with Radiotherapy and Chemotherapy

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Abstract

Background: To evaluate whether ABO-Rh blood groups have significance in the treatment response and prognosis in patients with non-metastatic breast cancer. Materials and Methods: We retrospectively evaluated files of 335 patients with breast cancer who were treated between 2005 and 2010. Demographic data, clinic-pathological findings, treatments employed, treatment response, and overall and disease-free survivals were reviewed. Relationships between clinic-pathological findings and blood groups were evaluated. Results: 329 women and 6 men were included to the study. Mean age at diagnosis was 55.2 years (range: 26-86). Of the cases, 95% received chemotherapy while 70% were given radiotherapy and 60.9% adjuvant hormone therapy after surgery. Some 63.0% were A blood group, 17.6% O, 14.3% B and 5.1% AB. In addition, 82.0% of the cases were Rh-positive. Mean follow-up was 24.5 months. Median overall and progression-free survival times were 83.9 and 79.5 months, respectively. Overall and disease-free survival times were found to be higher in patients with A and O blood groups ($p<0.05$). However rates did not differ with the Rh-positive group ($p=0.226$). In univariate and multivariate analyses, ABO blood groups were identified as factors that had significant effects on overall and disease-survival times ($p=0.011$ and $p=0.002$). Conclusions: It was seen that overall and disease-free survival times were higher in breast cancer patients with A and O blood groups when compared to those with other blood groups. It was seen that A and O blood groups had good prognostic value in patients with breast cancer.

Keywords: Breast cancer - ABO-Rh blood groups - treatment response - prognosis

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Introduction

Breast cancer is the most frequently seen malign tumor among women worldwide. It comprises 30% of all new cancer cases among women. Multimodal approach consisting of surgery, radiotherapy, chemotherapy and hormone therapy is of importance in the management of breast cancer (Ozmen, 2008; Iodice et al., 2010; Sozen and Benderli Cihan, 2012; Xing et al., 2014). Three-fourth of recurrences occurs within first 5 years after adjuvant therapies (Gates et al., 2012).

In recent years, value of many prognostic factors has been addressed in breast cancer. Factors such as performance status, stage, biological features of tumor and age are accepted to have prognostic value, while genetic factors including blood group antigens are being stressed in breast cancer (Sozen and Benderli Cihan, 2012; Xing et al., 2014).

Blood group is a somewhat cellular identity determined by antigenic structures on the surface of erythrocytes (Klimant et al., 2011, Xing et al., 2014). Many blood group systems have been identified by using this antigenic structure. Environmental factors don't have any effect on blood group development and it is a quantitative characteristic that exclusively represents genetic basis. ABO blood group system was discovered by Landsteiner at 19th century and it is the first discovered and most widely used blood group system. There is another blood group system based on presence or absence of Rh antigen. Today, ABO and Rh blood group systems are most widely used systems. In the literature, there are several studies on blood groups. These studies can be classified into two groups: studies directly addressing blood groups and its genetic, and those addressing relationship between genetics of blood group and benign or malign diseases (Holdsworth et al., 1985; Klimant et al., 2011; Miao et al., 2013).

ABO blood group genes have a differential distribution in the population. It is known that this is a risk factor for development of diseases. It has been reported that some cancer types are most frequently observed in subtypes of

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ABO blood groups. In the literature, many studies defined relationship between ABO blood groups and metastasis, prognosis, stage and histopathological diagnosis in several cancer types (Holdsworth et al., 1985; Iodice et al., 2010; Kos et al., 2014), although others showed no role (Urün et al., 2012; Unal et al., 2013; Utkan et al., 2013). In recent years, although there are published studies suggesting that blood groups are important in treatment response and prognosis in breast cancer, there is paucity in data in this field (Holdsworth et al., 1985; Klimant et al., 2011; Gates et al., 2012; Miao et al., 2013).

Primarily, it was aimed to investigate whether blood groups have prognostic value in breast cancer by using ABO blood groups that can be readily detected and represent genetic structure exclusively.

Materials and Methods

We retrospectively reviewed clinical data of 335 cases with non-metastatic breast cancer confirmed by histopathology and received chemotherapy, radiotherapy, and hormone therapy (according to receptor status) between 2005 and 2010. The following data were extracted from patient files: age, gender, menopausal status, stage, surgery type, adjuvant therapies (chemotherapy, radiotherapy, hormone therapy), histopathological data (histological subtypes, tumor size, axillary lymph node involvement, grade according to Scharf-Blood-Richardson grading system, hormone receptor status, and HER2/neu expression) and blood groups.

Staging was performed based on AJCC 2002 staging system. Presence of recurrence, date of recurrence, localization of recurrence and overall and disease-free survivals were extracted from patient files. Patients who didn't attend follow-up visit within prior 6 months were contacted by telephone. This study was planned in accordance to Helsinki Declaration, Patient Rights regulation and Ethic principles.

Chemotherapy

Decision regarding postoperative chemotherapy/ hormone therapy and/or radiotherapy was made by considering performance status, age, comorbid diseases. Chemotherapy was given to the patients with tumor diameter≥1cm and axillary lymph node≥1-positive. Chemotherapy regimens used were as follows: CMF (Cyclophosphamide, Methotrexate, 5-Fluorouracil), CAF (Cyclophosphamide, Doxorubicin, 5-Fluorouracil), CEF (Cyclophosphamide, Epirobucin, 5-Fluorouracil), AC (Doxorubicin, Cyclophosphamide) and docetaxel.

Radiotherapy

Radiotherapy was given to the patients with tumor diameter >5 cm and axillary lymph node≥3-positive. In these cases, radiotherapy was delivered to whole breast/ thorax wall and axillary and supraclavicular regions with gamma beam by using Co-60 device and 6 MV X-beam by using Linax device. Additional electron doses of 10 or 16 Gy were delivered to tumor bed and incision in patients at risk. Radiotherapy was delivered at a total dose of 50-66 Gy with 25-33 Gy fractions.

Hormone therapy and follow-up

Hormone therapy was initiated in the patients with positive estrogen and progesterone receptors. Tamoxifen and/or LHRH analogs were given to premenopausal patients while tamoxifen or aromatase inhibitors were given to postmenopausal patients. Follow-up visits were scheduled by 3-months interval within first year; biannually until end of year 5; and annually thereafter. Complete blood count, biochemical parameters, Ca 15-3 and CEA levels were measured biannually, while chest radiographs, mammography, abdominal sonography and bone scintigrapy were obtained annually.

Statistical analysis

Data were analyzed by using SPSS for Windows version 15.0 (SPSS Inc., Chicago, Illinos, USA). Normality was tested by using Kolmogrov-Simirnov method. Numeric variables were expressed as median and minimum-maximum values. Categorical variables were expressed as percents. Correlations between categorical variables were tested by using Pearson Chi-square and Monte Carlo tests. Overall survival was calculated as the time from diagnosis and death due to any reason, while disease free survival was calculated as the time from diagnosis to recurrence. Survival analysis was performed by using Kaplan-Meier curves. Univariate analysis was performed by using log-rank test, while multivariate analysis was performed by using Cox regression test. $p<0.05$ was considered as statistically significant.

Results

Table 1 presents demographic and clinic-pathological characteristics of the patients. Local recurrence (14 cases) or distant metastasis (45 cases) was detected during median follow-up of 19.5 months (mean: 24.5; range: 10 days-112 months). Forty-five cases died due disease-related or irrelevant causes. Multiple-organ metastasis was seen in 17 cases (38.0%), bone metastasis in 15 cases (33.0%), lung metastasis in 7 cases (15.0%), brain metastasis in 2 cases (4.4%), and other organ metastasis in 8 cases (8.8%). Median overall and progression-free survival times were 83.9 and 79.5 months. Five-and 7-years overall survival rates were 76% and 54%, while 5- and 7-years disease-free survival rates were 61% and 57%, respectively.

Table 2 presents distribution of ABO-Rh blood groups according to clinic-pathological features and results of analyses. A significant difference was found in histological grade among ABO blood groups ($p<0.008$). No significant difference was found among ABO-Rh blood groups regarding age, gender, menopausal status, body mass index (BMI), localization, stage, tumor diameter, lymph node involvement, pathology, histological grade, perivascular and lymphovascular invasion, hormone receptor status, HER2 positivity and adjuvant therapies used.

Table 3 presents disease-free and overall survival times according to ABO-Rh blood groups. Overall survival was found as 80.6 months in A blood group, 47.4 months in AB blood group, 59.0 months in B blood group and 84.7

Table 1. Demographic and Clinic-Pathological Characteristics of the Patients

Characteristic		Patients No (%)	Characteristic		Patients No (%)	Characteristic		Patients No (%)
Gender	Male	6 (1.8)	Lymph node status			Lymphovascular invasion		
	Female	329 (98.2)		0	110 (32.8)		No	138 (41.5)
Age (years)	Mean (range)	55.2 (26-86)		I	106 (31.6)		Yes	196 (58.5)
	<40	23 (6.9)		II	69 (20.6)	Surgery	Mastectomy	323 (96.4)
	40-60	207 (61.8)		III	46 (13.7)		Lumpectomy	12 (3.6)
	≥65	105 (31.3)		Unknown	4 (1.2)	Chemotherapy	Yes	318 (95)
Menopausal status	Premenopausal	130 (38.8)	Histologic grade				No	17 (5)
	Postmenopausal	199 (59.4)		I	70 (20.9)	Chemotherapy regime		
	No	6 (1.8)		II	158 (47.2)		CEF	106 (31.6)
BMI	<24.9	55 (16.4)		III	86 (25.7)		CAF	80 (23.9)
	25-30	94 (28.1)		Unknown	21 (6.3)		AC	53 (15.8)
	>30	186 (55.5)	ER status	Positive	184 (54.9)		The others	79 (23.5)
Tumor localization	Right	155 (46.3)		Negative	129 (38.5)		No	17 (5.0)
	Left	177 (52.8)		Unknown	22 (6.6)	Radiotherapy	No	100 (30)
	Bilateral	3 (0.9)	PR status	Negative	155 (46.3)		Yes	235 (70)
Tumor stage	I	39 (11.6)		Positive	173 (51.6)	Hormone replacement therapy		
	II	167 (50)		Unknown	7 (2.1)		Yes	204 (60.9)
	III	129 (38.5)	HER2 immunohistochemistry				No	131 (39.1)
Pathology	Invasive ductal	309 (92.2)		Negative	207 (61.8)	Blood group	A	211 (63.0)
	Inflematuar	12 (3.6)		Positive	106 (31.6)		B	48 (14.3)
	The other	14 (4.2)		Unknown	22 (6.6)		AB	17 (5.1)
Tumor size	I	68 (20.3)	Perinodal involvement				O	59 (17.6)
	II	199 (59.4)		No	118 (35.2)	Rh factor	Positive	275 (82)
	III	52 (15.5)		Yes	217 (64.8)		Negative	60 (18)
	IV	16 (4.8)						

*Abbreviations: BMI: body mass index; CAF: cyclophosphamide, Doxorubicin, 5-Fluorouracil; CEF: cyclophosphamide, epirobucin, 5-Fluorouracil; AC: doxorubicin, cyclophosphamide

Table 2. Distribution of ABO-Rh Blood Groups According to Clinic-Pathological Features and p value

Variable		A (n:211)	AB (n:17)	B (n:48)	O (n:59)	p value	Rh (-) (n:60)	Rh (+) (n:275)	p value
Gender	Male	4 (1.2)	0 (0)	1 (0.2)	1 (0.2)	0.95	0 (0)	6 (1.8)	0.507
	Female	207 (61.7)	17 8 (50.7)	47 (14.2)	58 (17.3)		60 (18)	268 (80)	
Age (years)	<40	13 (3.8)	1 (0.2)	4 (1.2)	5 (1.5)	0.866	21 (6.2)	2 (0.6)	0.391
	40-60	127 (38)	11 (3.2)	33 (9.6)	36 (10.7)		43 (12.8)	164 (49)	
	>65	71 (21.1)	5 (1.5)	11 (3.2)	18 (5.4)		15 (4.5)	90 (26.8)	
Menopausal status	Premenopausal	79 (23.5)	6 (1.8)	21 (6.2)	21 (6.2)	0.713	23 (6.8)	104 (31.0)	0.747
	Postmenopausal	128 (24)	11 (3.2)	25 (7.5)	35 (10.4)		36 (10.7)	163 (48.5)	
BMI	<24.9	37 (11.0)	4 (1.2)	6 (1.8)	8 (2.3)	0.718	10 (3.0)	45 (13.4)	0.629
	25-30	60 (18)	6 (1.8)	11 (3.2)	17 (5.0)		17 (5.0)	76 (22.6)	
	>30	114 (34)	7 (2.0)	31 (9.2)	34 (10.1)		33 (9.8)	153 (45.6)	
Tumor localization	Right	106 (31.6)	8 (2.4)	13 (3.9)	28 (8.3)	0.128	1 (0.3)	2 (0.6)	0.809
	Left	103 (30.7)	9 (2.7)	35 (10.4)	30 (9)		26 (7.7)	129 (38.5)	
Tumor stage	I	21 (6.2)	3 (0.9)	7 (2.0)	8 (2.3)	0.337	7 (2.0)	32 (9.5)	0.62
	II	115 (34.3)	8 (2.3)	22 (6.5)	22 (6.5)		34 (10.1)	132 (39.4)	
	III	75 (22.4)	6 (1.8)	19 (5.7)	29 (8.7)		19 (5.6)	110 (32.8)	
Pathology	Invasive ductal	194 (58)	15 (4.5)	45 (13.4)	55 (16.4)	0.61	57 (17.0)	252 (75.2)	0.866
	Inflematuar	10 (3.0)	1 (0.3)	0 (0)	1 (0.3)		2 (0.6)	10 (3.0)	
Tumor size	I	44 (13.1)	4 (1.2)	8 (2.3)	12 (3.5)	0.23	14 (4.2)	54 (16.1)	0.969
	II	127 (38)	9 (2.7)	32 (9.5)	31 (9.2)		35 (10.4)	163 (48.6)	
	III	31 (9.2)	1 (0.3)	6 (1.8)	14 (4.1)		9 (2.7)	43 (12.8)	
	IV	9 (2.7)	3 (0.9)	2 (0.6)	2 (0.6)		2 (0.6)	14 (4.1)	
Lymph node status	0	72 (21.4)	5 (1.5)	16 (4.8)	17 (5.0)	0.826	22 (6.5)	88 (26.2)	0.762
	I	70 (20.9)	6 (1.8)	14 (4.2)	16 (4.8)		208 (6.0)	86 (25.6)	
	II	40 (11.9)	3 (0.9)	12 (3.6)	14 (4.2)		138 (3.9)	56 (16.7)	
	III	27 (8.0)	2 (0.6)	6 (1.8)	11 (3.2)		5 (1.5)	41 (12.2)	
Histologic grade	I	55 (16.4)	2 (0.6)	5 (1.5)	8 (2.4)	0.008	10 (3.0)	60 (18.0)	0.705
	II	92 (27.4)	12 (3.5)	24 (7.1)	30 (9.0)		33 (9.8)	125 (37.3)	
	III	54 (16.1)	2 (0.6)	11 (3.2)	19 (5.6)		15 (4.5)	71 (21.2)	
ER status	Positive	119 (35.5)	8 (2.3)	28 (8.3)	29 (8.6)	0.369	34 (10.1)	150 (44.8)	0.751
	Negative	81 (22.8)	8 (2.3)	18 (5.3)	22 (6.5)		23 (6.9)	106 (31.6)	
PR status	Positive	108 (32.2)	8 (2.3)	31 (9.2)	26 (7.7)	0.472	25 (7.4)	130 (38.9)	0.479
	Negative	99 (29.5)	9 (2.6)	16 (4.8)	31 (9.2)		35 (10.4)	138 (41.1)	
HER2	Positive	62 (18.5)	6 (1.8)	14 (4.1)	24 (7.1)	0.71	39 (11.6)	168 (50.1)	0.542
	Negative	133 (37.4)	10 (3.0)	31 (9.2)	33 (9.8)		15 (4.5)	91 (27.1)	
Perinodal involvement	No	73 (21.8)	5 (1.5)	20 (6.0)	20 (6.0)	0.751	21 (6.2)	97 (28.9)	0.398
	Yes	138 (41.2)	12 (3.5)	28 (8.3)	39 (11.6)		39 (11.6)	138 (41.2)	
Lymphovascular invasion	No	93 (27.8)	4 (1.2)	21 (6.3)	21 (6.3)	0.285	22 (6.5)	117 (35.0)	0.356
	Yes	118 (35.2)	13 (3.9)	27 (8.0)	38 (11.3)		38 (11.3)	158 (47.1)	
Surgery	Mastectomy	203 (60.1)	16 (4.8)	47 (14.0)	52 (15.5)	0.895	58 (17.3)	265 (79)	0.909
	Lumpectomy	8 (2.4)	1 (0.3)	1 (0.3)	2 (0.6)		2 (0.6)	10 (3)	
Chemotherapy	Yes	197 (58.8)	16 (47.7)	48 (14.3)	56 (16.7)	0.373	57 (17)	260 (77.6)	0.972
	No	13 (3.9)	1 (0.3)	0 (0.0)	3 (0.9)		3 (0.9)	14 (4.2)	
Radiotherapy	No	62 (18.5)	6 (1.8)	15 (4.5)	17 (5.0)	0.953	18 (5.4)	82 (25.0)	0.307
	Yes	149 (44.5)	11 (3.2)	33 (9.8)	42 (12.5)		42 (12.5)	193 (57.6)	
Hormone therapy	Yes	125 (37.3)	10 (3)	31 (9.2)	38 (11.3)	0.968	34 (10.1)	170 (50.7)	0.084
	No	85 (25.3)	7 (2.0)	17 (5.0)	21 (6.2)		25 (7.5)	105 (31.3)	

months in O blood group. When overall survival time was assessed according to ABO blood groups, there was significant difference among groups (p<0.05; Figure 1a). Disease-free survival time was found as 79.6 months in A blood group, 51.9 months in AB blood group, 43.5 months in B blood group and 86.0 months in O blood group. When overall survival time was assessed according to ABO blood groups, there was significant difference among groups (p<0.05; Figure 1b). When considered according to Rh blood groups, it was found that overall and disease-free survival times were found to be higher in

Table 3. Overall and Disease-free Survive and p value According to ABO and Rh Blood Group of Patients

Variables	Patients No.	Overall Survival Survival month mean (95% CI)	p value	Disease-free survival Survival month mean (95% CI)	p value
Blood group					
A	211	80.6 (69.4-91.8)	0.047	79.6 (69.8-89.3)	0.01
AB	17	47.4 (32.2-62.7)		51.9 (38.7-65.0)	
B	48	59.0 (53.5-64.5)		43.5 (35.2-51.8)	
0	59	84.7 (78.4-91.2)		86.0 (75.7-97.5)	
Rh factor					
Positive	275	84 (74.3-93.8)	0.262	77.3 (69.1-85.5)	0.226
Negative	60	71.7 (64.1-79.4)		75.5 (65.0-85.9)	

*Abbreviations: CI: confidence interval

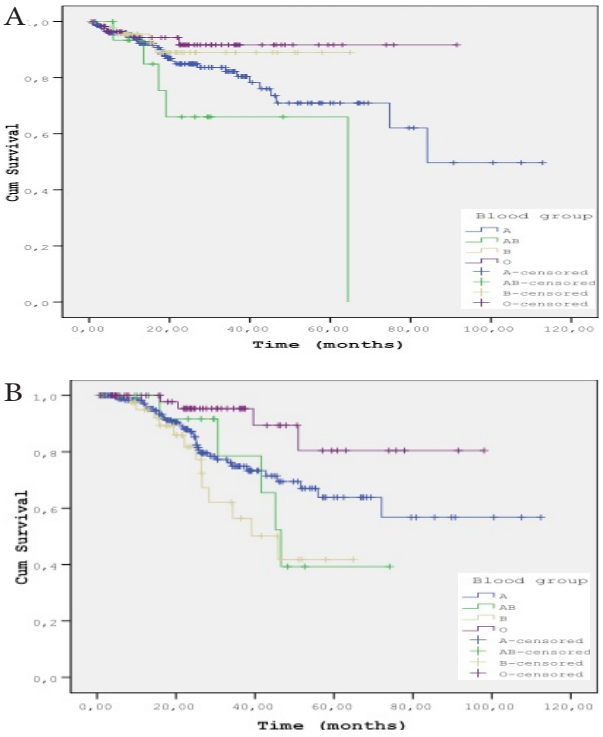

Figure 1. A) Overall and B) Disease-Free Survival According to ABO Blood Groups

Table 4. Univariate Analysis of Risk Factors for Overall and Disease-Free Survival

Risk factors		Overall Survival OR (95% CI)	p value	Disease-free Survival OR (95% CI)	p value
Blood group	0	Ref		Ref	
	AB	2.4 (0.8-7.0))	0.085	3.2 (1.1-9.0)	0.027
	B	5.5 (1.5-20.6)	0.011	4.3 (1.1-16.1)	0.029
	A	1.5 (0.4-6.4)	0.508	5.7 (1.8-17.7)	0.002
Rh factor (positive or negative)		0.6 (0.2-1.4)	0.268	0.6 (0.2-1.4)	0.231
Gender (male or female)		2.7 (0.6-11.3)	0.163	3.0 (0.9-9.8)	0.058
Age (years)	<40	Ref		Ref	
	40-60	1.8 (0.7-4.6)	0.22	1.2 (0.4-3.7)	0.705
	≥65	0.5 (0.3-1.1)	0.113	1.2 (0.7-2.3)	0.413
Menopausal status (premenopausal or postmenopausal)		1.0 (0.6-2.0)	0.795	0.3 (0.0-1.4)	0.136
BMI	<24.9	Ref		Ref	
	25-30	1.0 (0.4-2.2)	0.988	0.9 (0.4-1.9)	0.812
	>30	0.7 (0.4-1.5)	0.519	1.3 (0.8-2.3)	0.26
Tumor localization (left or right)	0.8	(0.4-1.5)	0.437	1.8 (0.2-13.7)	0.539
Tumor stage	I	Ref		Ref	
	II	0.9 (0.3-2.1)	0.827	0.3 (0.1-1.0)	0.063
	III	0.6 (0.3-1.2)	0.198	0.7 (0.4-1.2)	0.275
Pathology(invasive ductal or inflematuar)		0.3 (0.1-0.8)	0.029	0.7 (0.3-1.9)	0.576
Tumor size	I	Ref		Ref	
	II	1.1 (0.2-4.9)	0.878	0.7 (0.1-3.4)	0.742
	III	0.6 (0.1-2.6)	0.625	0.9 (0.2-3.8)	0.927
	IV	0.3 (0.1-2.6)	0.176	0.9 (0.2-4.3)	0.943
Lymph node status	0	Ref		Ref	
	I	0.5 (0.2-1.3)	0.17	0.9 (0.1-4.0)	0.945
	II	0.8 (0.3-2.0)	0.63	0.7 (0.1-3.2)	0.674
	III	0.8 (0.3-2.2)	0.724	0.9 (0.2-4.4)	0.967
Histologic grade	I	Ref		Ref	
	II	1.4 (0.3-6.6)	0.663	6.2 (0.8-46.9)	0.076
	III	1.9 (0.4-8.3)	0.352	6.4 (0.8-47.3)	0.066
ER status (positive or negative)		1.0 (0.3-3.5)	0.925	0.4 (0.2-1.0)	0.058
PR status (positive or negative)		1.5 (0.8-2.6)	0.206	1.1 (0.1-8.1)	0.922
HER2 immunohistochemistry (negative or positive)		0.8 (0.3-2.3)	0.702	0.9 (0.3-2.7)	0.947
Perinodal tutulum (no or yes)		0.5 (0.2-1.1)	0.106	1.0 (0.6-1.7)	0.907
Lenfovasküler invazyon (no or yes)		0.7 (0.4-1.4)	0.398	0.9 (0.5-1.5)	0.83
Surgery (mastectomy or lumpectomy)		0.7 (0.1-5.7)	0.813	2.5 (0.9-7.1)	0.074
Chemotherapy (no or yes)		0.5 (0.2-1.5)	0.255	0.9 (0.3-2.9)	0.887
Radiotherapy (no or yes)		0.7 (0.3-1.5)	0.374	1.1 (0.6-2.0)	0.559
Hormone therapy (no or yes)		0.9 (0.5-1.6)	0.641	1.8 (1.0-3.2)	0.045

Table 5. Multiivariate Analysis of Risk Factors for Overall and Disease-free Survival

Risk factors		Overall survival		Disease-free survival	
		OR (95% CI)	p value	OR (95% CI)	p value
Blood group	0	Ref		Ref	
	AB	2.7 (0.9-7.8)	0.059	3.5 (1.2-9.7)	0.019
	B	5.7 (1.5-21.2)	0.01	4.7 (1.3-17.3)	0.022
	A	1.7 (0.4-6.8)	0.459	5.5 (1.8-17.2)	0.003
Hormone therapy (no or yes)					
		-	-	1.8 (1.0-3.2)	0.042
Pathology (invasive ductal or inflematuar)					
		1.7 (1.1-2.8)	0.015	-	-

Rh-positive group when compared to Rh-negative group, but the difference didn't statistical significance (p=0.262 and p=0.226).

Tables 4 and 5 present results of univariate and multivariate analysis overall and disease-free survival. In univariate analysis, ABO blood groups and pathologic subtype were identified as factors that had significant effect on overall survival; ABO blood groups and hormonotherapy had significant effect on disease-survival ($p<0.05$). These factors (ABO blood, pathologic subtype and hormonotherapy) remained to be significant in multivariate analysis.

Discussion

Several aspects of clinic-pathological correlations of ABO-Rh blood group with many diseases, particularly cancers, have been subject of investigation from beginning of the century (Iodice et al., 2010; Gates et al., 2012; Mortazavi et al., 2014). The fact that there were discrepancies in the temporal data of blood group investigations regarding material, character, genetic and experimental applications indicates that blood groups remain to be mysterious. One can suggest that further comprehensive studies with different designs are needed to obtain consistent and concrete results. Thus, a different perspective was used to investigate the relationship between ABO blood groups and breast cancer in the present study. It was aimed to detect value of blood groups in treatment response and prognosis in breast cancer.

In breast cancer, demographic characteristics such as age, menopausal status and ethnicity, tumor characteristics such as tumor size, axillary lymph node status, and histopathological subtype, and biomarkers such as oncogene, tumor suppressor genes, growth factors and proliferation measures are known to be potential prognostic factors (Iodice et al., 2010; Klimant et al., 2011; Sozen and Benderli Cihan, 2012; Miao et al., 2013; Xing et al., 2014). Unfortunately, based on current understanding, it is impossible to precisely determine patients who would recover by local treatment or those who would die due to recurrence despite treatment; thus, there is an ongoing effort to identify novel prognostic factors. It has been thought that ABO-Rh blood groups, a genetic feature, have prognostic value in patients with breast cancer. However, data are scarce in this field. In the present study, it was aimed to clarify relationship between known blood group phenotypes and above-mentioned prognostic factors and to enable formerly detection of risk groups thought to be relevant.

In our study, it was seen that the highest percent distribution was in A blood group, while lowest percent distribution in AB blood group. The relationship between breast cancer and blood groups were first described by Aird et al. In that study, it was reported that there was no association between breast cancer and blood groups (Aird et al., 1954). Miao et al. evaluated blood group distribution in 9665 patients with breast cancer and compared with 244,768 healthy controls. Authors reported that breast cancer incidence was similar among all ABO blood groups (Miao et al., 2013). In a study by Hems and Anderson, it was reported that A blood group was more commonly seen in patients with breast cancer (Hems, 1970; Anderson et al., 1985). In the study by Tryggvadottir et al., it was reported that B blood group type was 2 fold more common among cases with familial breast cancer when compared to sporadic cases (Tryggvadottir et al., 1988). Iodice et al. evaluated blood group distribution in 15,359 cancer patients and found that breast cancer incidence was higher among patients with O blood group but the difference didn't reach statistical significant (p=0.60) (Iodice et al., 2010). In another study by Cihan et al, the distribution of ABO-Rh blood groups in 255 patients with skin cancer was compared to those obtained from 25,071 healthy blood donors. In the control group, the most frequent blood group was A blood group (44.3%); followed by O blood group (31.5%), B blood group (16.1%) and AB blood group (8.1%). In the patient group, the most frequent blood group was A blood group (50.2%); followed by O blood group (26.3%), B blood group (16.1%) and AB blood group (7.5%). There was significant difference between patient and control groups regarding distribution of ABO-Rh blood groups. Skin cancer was more commonly observed in A blood group (Cihan et al., 2013). When our study was compared to control group of our previous study, it was seen that distribution of blood groups in the breast cancer were in line with control group. In addition, our results were consistent with those reported by Guleria et al., Anderson et al. (1985) and Hems in study.

In our study, overall and disease-free survival was highest in O blood group; followed by A blood group in breast cancer. This difference was found to be statistically significant ($p<0.05$). Although there are discrepant results in the literature, Guleria et al. demonstrated that breast cancer was more prevalent and associated with poor prognosis in women with A blood group (Guleria et al., 2005). In a study by Gates et al., it was reported that there was no association between ABO blood groups and breast cancer risk or survival (Gates et al., 2012). In a study on 426 patients with breast cancer by Klimant et al., A blood group was identified in 198 patients (46.5%), while O blood group in 163 (38.3%), B blood group in 43 (10.1%) and AB blood group in 22 patients (5.2%). Blood group distribution in patients with breast cancer didn't differ from that in general population (p=0.08). However, there was a trend towards higher rates of B blood group and lower rates of AB blood group. In that study, 5-years overall and disease free survivals were 93.0 months in AB blood group, 80.6 months in A blood group, 79.6 months in O group and 74.5 months in B blood group. Authors

concluded that there was no significant difference in overall and disease-free survivals among blood groups. Also, no correlation was reported between blood group type and HER2/neu, ER and PR status (Klimant et al., 2011). In our study, it was seen that survival was higher in patients with A and O blood groups when compared to other blood groups. In agreement with the results of Klimant et al. (2011); Gates et al. (2012) no correlation was observed between ABO-Rh blood groups and age, menopausal status, BMI, localization, stage, tumor diameter, lymph node involvement, perivascular and lymphovascular invasion, hormone receptor status and HER2 positivity (Klimant et al., 2011; Gates et al., 2012).

In our study, it was found that overall and disease free survivals were higher in Rh-positive patients when compared to Rh-negative patients, but the difference didn't reach statistical significance. There is limited number of studies about relationship of Rh factor to cancer, reporting inconsistent results. In a study by Ronco et al., it was reported that there was higher risk for breast cancer in Rh-negative population (Ronco et al., 2009), while no such relationship was found in the studies by Dede et al. and Stamatakos et al. Ronco et al. reported breast cancer risk was higher by 50% in Rh-negative patients when compared to Rh-positive patients (Ronco et al., 2009; Stamatakos et al., 2009; Dede et al., 2010). In the study by Stamatakos et al., it was reported that metastasis risk was 4.2 fold higher in Rh-negative patients with breast cancer when compared to Rh-positive patients with breast cancer (Stamatakos et al., 2009).

In conclusion, in our study, it was seen that breast cancer is more common in patients with A and Rh-positive blood groups. It was seen that overall and disease-free survival times were higher in breast cancer patients with A and O blood groups when compared to those with other blood groups. Further comprehensive studies are needed to elucidate relationship between ABO-Rh blood groups and breast cancer. It can be suggested that our study will provide a basis for future studies in this topic.

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