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Research Article

The Prevalence and Prognostic Relevance of ABO/Rh Blood Groups in Metastatic Breast Cancer Patients Undergoing Cyclin-Dependent Kinase 4/6 Inhibitors Therapy

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Abstract

Objectives: Breast cancer (BC) is the most commonly malignancy in women. The emergence of cyclin-dependent kinase inhibitors (CdK 4/6i) has significantly improved prognosis. Until now, no predictive factor of response to CdK4/6i has been identified. This study investigates the relationship between ABO and Rhesus (D) groups and the therapeutic response to CdK4/6i.

Methods: This retrospective study registered records of mBC treated with CdK 4/6i at the Kartal Dr. Lutfi Kirdar City Hospital.

Results: The study comprised 185 metastatic BC patients. During the study period, 32 patients (17.3%) died. The median overall survival (OS) was 18.3 months. The A group had the highest number of deaths (n=16), while the B group had the highest death rate proportionally (23.0%). Interestingly, no deaths were observed in the AB group. Disease progression was observed in 84 patients (45.4%). An analysis of the average progression-free survival (PFS) showed that patients with group O was PFS of 37.8 months (95% Confidence Interval (CI): 31.0-44.6), group A was 19.7 months (95% CI: 16.6-22.8), group B was 19.6 months (95% CI: 14.3-24.8), and group AB was 14.2 months (95% CI: 28.5-36.8). No statistically significant difference was observed when an OS (p=0.23) and PFS (p=0.138) analysis was performed according to ABO groups. In the univariate analysis, the Rh factor did not serve as a prognostic factor on either PFS or OS.

Conclusion: We found no prognostic effect of blood group or Rh status on overall survival and progression-free survival in patients.

Keywords: Cyclin-dependent kinase inhibitors (CdK 4/6i), ABO blood and Rhesus (D) groups ,Oveall Survival, Progression Free Survival

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Breast cancer (BC) is the leading cause of cancer death in women worldwide. In the United States, breast cancer is the most common female cancer and the second most common cause of cancer-related death in women.[1] Approximately 6-10% of BC cases are de novo metastatic at diagnosis, and 25-30% exhibit metastatic recurrence.[2] Around 70% of BC cases are hormone receptor-positive (HR+) and human epidermal growth factor receptor-2 neg-

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ative (HER2-). Endocrine therapy (ET) is the primary treatment for patients with HR+/HER2- metastatic BC (mBC). The emergence of cyclin-dependent kinase inhibitors (CdK 4/6i) has significantly improved prognosis, now the gold standard for first-line treatment of HR+/HER2- mBC without extensive visceral involvement.[3-6] Prognostic factors are vital in predicting outcomes and determining the most suitable treatment for each patient. However, until now, no predictive factor of response to CdK4/6i and ET has been identified, and novel factors are needed to personalize first-line treatment.

ABO blood group antigens, expressed on red blood cell membranes and surfaces of various normal and pathological cells, have recently been the subject of growing research interest due to their potential correlation with certain human cancers. In particular, a relationship has been noted between gastric and pancreatic cancer risk.[7-10] Nevertheless, evidence of a relationship with BC has been inconsistent,[11-15] with earlier studies generally reporting no association.[11-13] However, two investigations revealed a correlation between blood group A or B and an elevated risk of familial BC.[14,15] As with studies on the ABO blood group and BC survival, associations with the Rh factor have been similarly inconsistent.[11,12,16-20]

Certain malignant breast tumors display a loss of ABO antigen expression, whereas benign lesions demonstrate varied antigen expression,[21,22] suggesting a potential role of ABO blood group antigens in breast carcinogenesis. Some research has also indicated a possible correlation between blood group antigen expression and prognostic factors among BC patients.[23,24]

The literature has scarce data regarding the relationship and prognostic significance of ABO/Rh groups in mBC. This study investigates the relationship between ABO blood and Rhesus (D) groups and the therapeutic response to CdK4/6i in mBC patients.

Methods

This retrospective study registered records of mBC treated with CdK 4/6i at the Kartal Dr. Lutfi Kirdar City Hospital from 2018 to 2022. Patients over 18 with clinically identified primary BC and no concurrent malignancies were included. Demographic data, tumor histopathology, presence of metastasis, tumor localization, ABO blood group and Rh group were assessed.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Descriptive statistics were used to evaluate frequency distributions of the collected data and examine associations with specific ABO blood type/Rh factor. Chi-square analysis was used for data comparison among different blood type categories. Overall Survival (OS), the duration from CdK4/6i initiation to death from any cause, was assessed using Kaplan-Meier graphical analysis for patient populations according to ABO blood type or Rh factor status. Progression-Free Survival (PFS), determined as the period from the initiation of CdK 4/6i therapy to the date of radiological progression or the most recent outpatient follow-up date, was also evaluated. Cox regression models were created to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for each blood type/Rh factor category. The significance level was established as ≤0.05.

Ethical Aproval

All procedures conducted in this study involving human participants complied with the ethical standards of the institutional and national research committee, in addition to the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical norms. The Ethics/Institutional Review Board of the Kartal Dr. Lütfi Kirdar City Hospital, Istanbul, Turkey, approved the research—Approval Number: 2023/514/250/2, 29.05.2023.

Results

The study comprised 185 metastatic HR+/HER2- patients. At the time of diagnosis, the median age was 55 years (range: 44–66 years). The median follow-up duration amounted to 21.8 months. Invasive ductal carcinoma emerged as the most prevalent histological type of tumor, presenting in 47.6% of cases. Among the patients, 40% were initially diagnosed at stage 4 of the disease. 69.2% (n=128) of the patients were postmenopausal. The number of patients using ribociclib (n=97) and palbociclib (n=88) was similar. Most patients (56.8%) were employing the treatment as first-line therapy, and partial remission was the most frequently achieved response, observed in 62.7% of cases. The baseline demographic data, clinicopathological factors, treatment modalities and outcomes of the patients are displayed in Table 1.

The allocation of patients according to their ABO/Rh groups exhibited a normal distribution. Out of the patient population, 147 individuals (79.5%) were Rh-positive. Furthermore, upon analysis of the clinicopathological characteristics of the patients and the distribution of blood groups, no significant disparities were observed between the ABO/Rh blood groups and variables such as age, histological characteristics (ER, PR, HER2/neu receptor status, grade, Ki-67

Table 1. Baseline demographic data, clinicopathological factors, treatment modalities and outcomes of the patients

Variable All patient (n=185)	Findings n, (%)	Variable All patient (n=185)	Findings n, (%)
Mean Age at Diagnosis, years (±SD)	55.71 (11.74)	Grade (n=155)	
Blood Group		I	8 (5.2)
O	66 (35.6)	II	123 (79.4)
A	78 (42.2)	III	24 (15.4)
B	26 (14.1)	Disease status	
AB	15 (8.1)	Recurren metastatic	111 (60.0)
Rh Group		De novo metastatic	74 (40.0)
Positive	147 (79.5)	CDK 4/6i	
Negative	38 (20.5)	Ribociclib	97 (52.4)
Age >50 Years	114 (61.6)	Palbociclib	88 (47.6)
Menopausal status (n=184)		Hormone therapy	
Pre-menopause	56 (30.4)	Letrozole	100 (54.1)
Post-menopause	128 (69.6)	Fulvestrant	85 (45.9)
ECOG Status		CDK 4/6i response (n= 178)	
0	118 (63.8)	Complete Remission	2 (1.1)
1	57 (30.8)	Partial Remission	116 (65.3)
2	9 (4.9)	Stable Remission	24 (13.5)
3	1 (0.5)	Progressive Disease	36 (20.1)
Histological type		CDK 4/6i treatment line	
Invasive ductal carcinoma	88 (47.5)	First line	105 (56.7)
Invasive lobular carcinoma	19 (10.3)	Second line	56 (30.3)
Infiltrating carcinoma (NOS)	71 (38.4)	Third and beyond	24 (13.0)
Others*	7 (3.8)	Presence of progression	
ER status % (n=178)		Presence	84 (45.4)
<40	8 (4.5)	Absence	101 (54.6)
40-90	56 (31.5)	Latest status	
>90	114 (64.0)	Exitus	32 (17.3)
PR status		Alive	153 (82.7)
Positive	163 (88.1)	B antigen status	
Negative	22 (11.9)	0 and A group	144 (77.8)
HER2 overexpression (n=30)		B and AB group	41 (22.2)
Score 0	15 (50.0)	A antigen status	
Score 1	9 (30.0)	0 and B group	93 (50.3)
Score 2 fish negative	6 (20.0)	A and AB group	92 (49.7)
Ki-67 proliferation index (n=123)		Antigen presence	
<30	75 (60.9)	0 group	66 (35.7)
>30	48 (39.1)	A, B, and AB group	119 (64.3)

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; CdK 4/6 i: cyclin-dependent kinase 4 and 6 inhibitor; ECOG: Eastern Cooperative Oncology Group; *others: tubular carcinoma, medullary carcinoma and mucinous carcinoma.

index, and histological subtype), and ECOG performance scores. The distribution of ABO/Rh blood types among patients is presented in Table 2.

During the study period, 32 patients (17.3%) died. The median OS was 18.3 months (0.59-59.3). Of the patients, 105 received cyclin-dependent kinase inhibitors (CDKi) as first-line treatment in the metastatic setting. In contrast, 56 patients were administered these inhibitors during the second line of treatment, and 24 patients used them during the third line of treatment or beyond.

No statistically significant difference was observed when a survival analysis was conducted based on the ABO blood groups (p=0.230) and Rh status (p=0.138). However, numerically, the A group had the highest number of deaths (n=16), while the B blood group had the highest death rate proportionally (23.0%). Interestingly, no deaths were ob-

Table 2. Patient and tumor characteristics for 185 patients with metastatic breast cancer by specific ABO blood type and Rh factor

Factor		AB, n (%)	B, n (%)	O, n (%)	p	Rh+, n (%)	Rh-, n (%)	p
Age (years)								
≥50	50 (64.2)	9 (60.0)	22 (84.7)	41 (62.2)	0.186	96 (65.3)	26 (68.4)	0.842
<50	28 (35.8)	6 (40.0)	4 (15.3)	25 (37.8)		51 (34.7)	12 (31.6)	
ECOG performance score								
0	48 (61.5)	9 (60.0)	17 (65.4)	44 (66.6)	0.470	92 (62.6)	26 (68.4)	0.550
1	26 (33.3)	6 (40.0)	6 (23.0)	19 (28.8)		48 (32.6)	9 (23.7)	
2	4 (5.2)	0 (0.0)	2 (7.8)	3 (4.6)		6 (4.1)	3 (7.9)	
3	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)		1 (0.7)	0 (0.0)	
Histological type								
Infiltrative Ductal Carsinoma	37 (47.5)	5 (33.3)	12 (46.2)	32 (48.5)	0.994	68 (46.3)	20 (52.7)	0.061
Infiltrative Lobular Carsinoma	7 (9.0)	0 (0.0)	3 (11.6)	8 (12.1)		16 (10.9)	3 (7.9)	
Infiltrating carcinoma (NOS)	31 (39.7)	10 (66.7)	7 (26.9)	23 (34.9)		60 (40.8)	11 (28.9)	
Others*	3 (3.8)	0 (0.0)	4 (15.3)	3 (4.5)		3 (2.0)	4 (10.5)	
ER percentage (n=178)								
<40	2 (2.7)	1 (6.6)	1 (4.2)	4 (6.3)	0.692	5 (3.5)	3 (8.3)	0.415
40-90	22 (29.3)	7 (46.7)	6 (25.0)	21 (32.8)		44 (31.0)	12 (33.3)	
>90	51 (68.0)	7 (46.7)	17 (70.8)	39 (60.9)		93 (65.5)	21 (58.4)	
PR status								
Positive	68 (87.2)	11 (73.3)	24 (92.3)	60 (90.9)	0.249	127 (86.4)	36 (94.7)	0.157
Negative	10 (12.8)	4 (26.7)	2 (7.7)	6 (9.1)		20 (13.6)	2 (5.3)	
HER2 overexpression (n=30)								
Score 0	5 (45.4)	0 (0.0)	3 (50.0)	7 (70.0)	0.523	12 (48.0)	3 (60.0)	0.468
Score 1	3 (27.3)	2 (66.7)	2 (33.4)	2 (20.0)		7 (28.0)	2 (40.0)	
Score 2 fish negative	3 (27.3)	1 (33.3)	1 (16.6)	1 (10.0)		6 (24.0)	0 (0.0)	
Grade (n=155)								
I	6 (8.7)	0 (0.0)	0 (0.0)	2 (3.8)	0.342	6 (4.8)	2 (6.7)	0.619
II	53 (76.8)	8 (66.7)	18 (85.7)	44 (83.0)		98 (78.4)	25 (83.3)	
III	10 (14.5)	4 (33.3)	3 (14.3)	7 (13.2)		21 (16.8)	3 (10.0)	
Ki-67 proliferation index (n=123)		0.463		0.482				
<20	15 (28.3)	2 (20.0)	2 (13.3)	15 (33.3)		28 (28.3)	6 (25.0)	
>20	38 (71.7)	8 (80.0)	13 (86.7)	30 (66.7)		71 (71.7)	18 (75.0)	

n (%) denotes the number of patients and the corresponding column percentage in each category; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; CdK 4/6 i: cyclin-dependent kinase 4 and 6 inhibitor; ECOG: Eastern Cooperative Oncology Group; *others: tubular carcinoma, medullary carcinoma and mucinous carcinoma; Chi-square or Fishers' exact test was used; P values> 0.05 for all comparisons.

served in the AB blood group. In the univariate analysis, the ABO blood groups were not prognostic factors for OS (Fig. 1a and Table 3).

Disease progression was observed in 84 patients (45.4%) during the study period. An analysis of the average PFS showed that patients with blood group O had a PFS of 37.8 months (95% Confidence Interval (CI): 31.0-44.6), blood group A had a PFS of 19.7 months (95% CI: 16.6-22.8), blood group B had a PFS of 19.6 months (95% CI: 14.3-24.8), and blood group AB had a PFS of 14.2 months (95% CI: 28.5-36.8). In the univariate analysis, the ABO blood groups were not prognostic factors for PFS (p=0.138) (Fig. 1b and Table 3).

The average OS for patients with Rh-positive status was 48.3 months (95% CI: 44.6-51.9), whereas the OS for patients with Rh-negative status was 29.1 months (95% CI: 26.5-31.7 p=0.261) Among Rh-positive patients, 28 deaths were observed, while four deaths occurred among Rh-negative patients. Regarding average PFS, Rh-positive patients had a PFS of 31.9 months (95% CI: 27.3-36.4), whereas Rh-negative patients had a PFS of 21.4 months (95% CI: 17.2-25.6 p=0.332). Disease progression was observed in 70 Rh-positive patients and 14 Rh-negative patients. In the univariate analysis, the Rh factor did not serve as a prognostic factor on either PFS or OS (Figs. 2a and 2b).

Additionally, we evaluated the impact on survival of blood groups containing the B antigen versus those not having

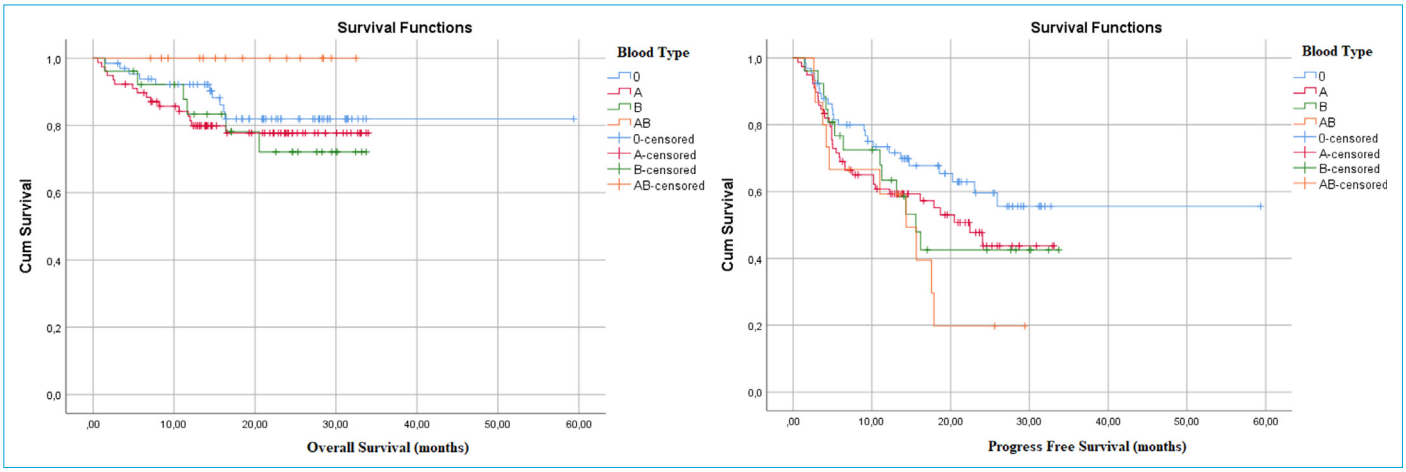

Figure 1. (a) Kaplan–Meier survival curves for OS by ABO blood groups. **(b)** Kaplan–Meier survival curves for PFS by ABO blood groups.

Table 3. OS and PFS data by ABO blood group and Rh status

	A (n=78)	AB (n=15)	B (n=26)	O (n=66)	p
Exitus, n (%)	16 (20.5)	0 (0.0)	6 (23.0)	10 (15.1)	0.230
6-Month Overall Survival (OS)	89.7	100	92.1	93.8	
12-Month OS	81.4	100	83.4	92.2	
24-Month OS	77.7	100	72.1	81.9	
Progression, n (%)	37 (47.4)	10 (66.6)	13 (50.0)	24 (36.3)	0.138
6-Month Progression-Free Survival (PFS)	69.0	66.7	76.7	80.0	
12-Month PFS	60.8	59.3	63.4	73.4	
24-Month PFS	47.7	19.8	42.6	59.6	
36-Month PFS	43.8	19.8	42.6	55.6	
	Rh+ (n=147)	**Rh- (n=38)**	**p**		
Exitus, n (%)	28 (19.0)	4 (10.5)	0.261		
6-Month Overall Survival (OS)	92.5	92.1			
12-Month OS	85.7	92.1			
24-Month OS	77.8	89.2			
Progression, n (%)	70 (47.6)	14 (36.8)	0.332		
6-Month Progression-Free Survival (PFS)	72.4	78.9			
12-Month PFS	62.6	76.3			
24-Month PFS	48.4	69.9			
36-Month PFS	45.2	44.8			

Percentages are given as column percentages; * Overall and progression-free survival were calculated using Kaplan-Meier analysis. A p-value < 0.05 was considered statistically significant.

the B antigen, blood groups containing the A antigen versus those not having the A antigen, and O blood group versus non-O blood groups (Figs. 3a-c). We did not find any statistically significant impact (Table 4).

In addition, we examined the comparison of the B antigen blood group and B antigen-free blood group, A antigen blood group and non-A antigen blood group, and O blood group and non-O blood group regarding the progression effect (Figs. 4a-c). We could not detect a statistically significant result (Table 5).

Discussion

In our study, we found fundamental data concerning the distribution of blood groups and their prognostic significance in patients with metastatic breast cancer (MBC). Although we observed a higher prevalence of A and O blood groups in MBC patients, our data indicates they do not serve as prognostic factors for OS and PFS in women treated with CdK4/6 inhibitors (CdK4/6i) and endocrine therapy (ET) for metastatic HR+/HER2- breast cancer.

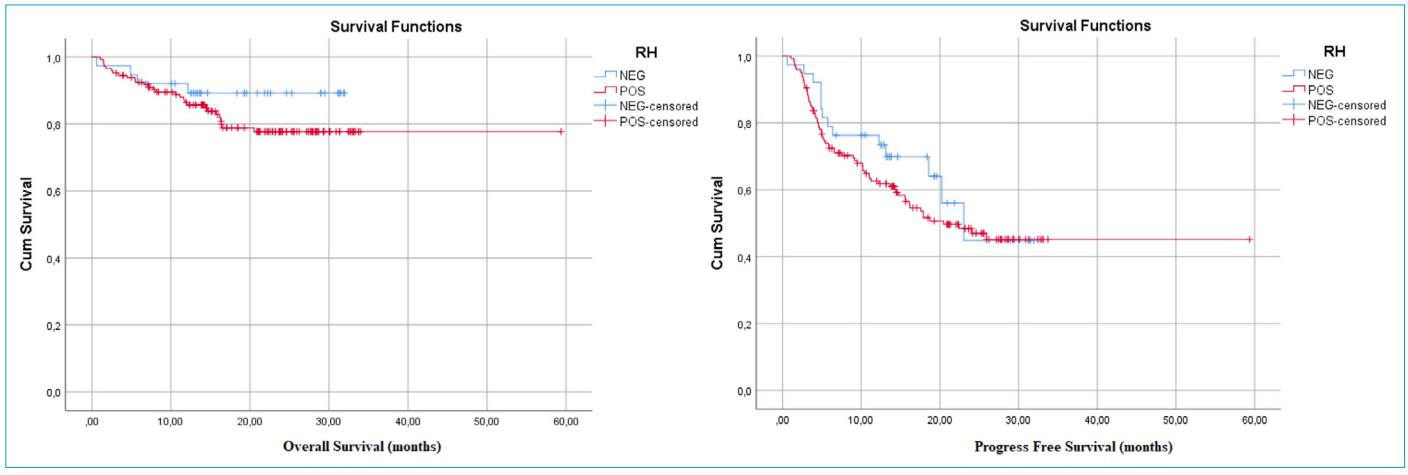

Figure 2. (a) Kaplan–Meier survival curves for OS by Rh factors. **(b)** Kaplan–Meier survival curves for PFS by Rh factors.

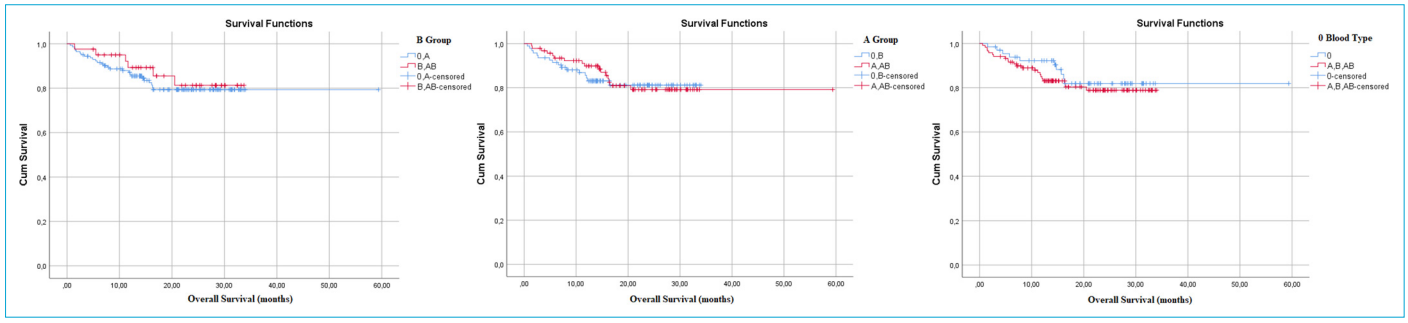

Figure 3. (a) Kaplan–Meier survival curves for OS by O, A groups and B, AB blood groups. **(b)** Kaplan–Meier survival curves for OS by O, B groups and A, AB blood groups. **(c)** Kaplan–Meier survival curves for OS by O group and non-O blood groups.

A retrospective analysis of 1,001 cases of invasive breast cancer by Holdsworth et al. demonstrated that blood types AB and B could be classified as higher risk compared to types O and A. When the four blood types were analyzed as separate groups, a significantly higher local recurrence rate was identified in patients with blood type AB. However, when blood types AB and B were combined as a higher-risk group, a significantly increased incidence of breast cancer and poorer OS compared to types O and A combined became evident.[18] But, in the blood group analysis performed in our study, antigen status was not associated with OS. Our analysis of survival based on blood groups and Rh status did not reveal a statistically significant difference. However, among the 32 patients who died, 16 belonged to group A, 10 belonged to group 0 and 6, representing 23% of group B, also died. No deaths occurred in the AB blood

Table 4. OS data by ABO blood group antigen presence

Antigen Presence	Overall Survival (months)	p
B Antigen		
0 and A Group	48.9 (45.2-52.5)	0.579
B and AB Group	29.7 (26.8-32.6)	
A Antigen		
0 and B Group	28.9 (26.7-31.2)	0.847
A and AB Group	49.3 (44.9-53.7)	
Presence of any antigen		
0 Group	50.5 (45.6-55.5)	0.476
A, B, AB Group	28.6 (26.6-30.6)	

* Overall and progression-free survival were calculated using Kaplan-Meier analysis. A p-value < 0.05 was considered statistically significant.

Table 5. PFS data by ABO blood group antigen presence

	Progression-Free Survival (months)	p
Presence of B antigen		
0 and A group	34.2 (29.4-38.9)	0.156
B and AB group	17.9 (3.9-22.0)	
Presence of A antigen		
0 and B group	18.9 (16.1-21.7)	0.106
A and AB group	35.9 (30.2-41.6)	
Presence of any antigen		
0 group	37.8 (31.0-44.6)	0.052
A, B, AB group	19.3 (16.8-21.8)	

* Overall and progression-free survival were calculated using Kaplan-Meier analysis. A p-value < 0.05 was considered statistically significant.

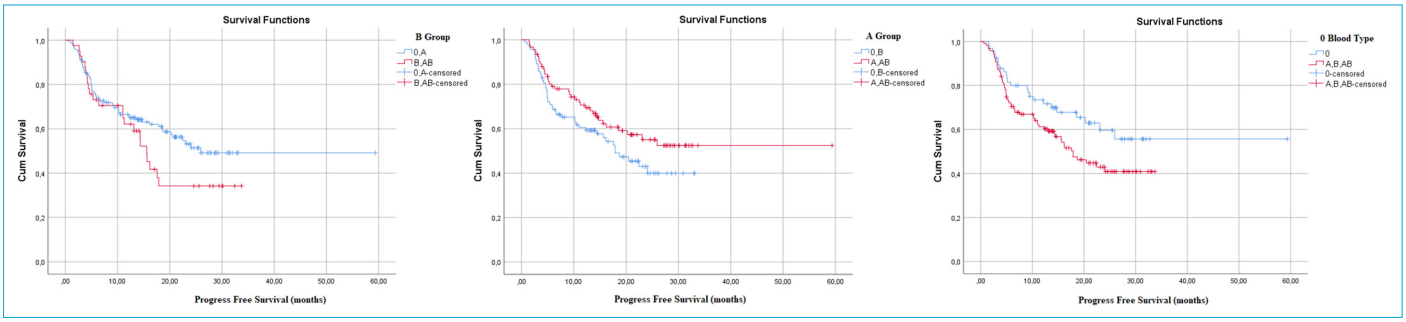

Figure 4. (a) Presents Kaplan-Meier survival curves for progression-free survival (PFS) categorized by O, A groups versus B, AB blood groups. **(b)** Persents Kaplan-Meier survival curves for PFS by O, B groups versus A, AB blood groups. **(c)** Persents Kaplan-Meier survival curves for PFS by O group and non-O blood groups.

group. Of the patients, 28 (19.0%) who were Rh positive and 4 (10.5%) who were Rh negative died. When examining the 24-month survival rate, 77.8% of Rh-positive and 89.2% of Rh-negative patients were alive. However, in the univariate analysis, ABO/Rh blood was not identified as a prognostic factor on OS.

A separate study of 1,138 patients with invasive breast cancer further showed no association between ABO genotype and the incidence of any breast cancer subgroups, including invasive, ductal, or hormone receptor-positive tumors.[25] Our study investigated the relationship between patients' blood group distribution and their clinicopathological features. Data on the relationship between breast cancer clinicopathological features and ABO/Rh blood group is limited. The type, grade, stage, and hormonal state of breast cancer showed no significant relationships with ABO blood grouping, according to the retrospective study published by Serkan et al.[26] Similarly, we could not find an association between blood group characteristics and the age at diagnosis, performance scores, and histopathologic features of MBC patients.

Although the significant improvement in prognosis brought about by the advent of CdK 4/6 inhibitors, no prognostic or predictive factors for the response have been identified, recent studies like those of Kanaoka et al., who examined absolute lymphocyte count (ALC), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) in patients with HR+ HER2- advanced breast cancer treated with the CDK4/6 inhibitors, abemaciclib, and palbociclib, suggested that ALC is an independent prognostic factor for HR+/HER2- advanced breast cancer patients treated with these CDK4/6 inhibitors.[27] Rottier et al. evaluated the pre-treatment NLR of 126 patients using CdK 4/6 inhibitors. They found a high NLR associated with worse PFS and OS in HR+ HER2- mBC patients treated with first-line CdK4/6 inhibitors.[28]

In our study of 185 patients using CdK4/6 inhibitors, we assessed PFS according to blood groups and Rh statuses. Of the 84 patients who progressed, 37 were of blood group A, and half of those with blood group B progressed. Among Rh-positive patients, 47.6% progressed, compared to 36.8% of Rh-negative patients. Univariate analysis did not show statistical significance. When looking at the 24-month PFS, Rh+ patients had better outcomes, with 48.4% not progressing, although this was not statistically significant.

This study's limitation was its retrospective design. In addition, some data were missing, which could have biased the statistical analysis.

Conclusion

We found no prognostic effect of blood group or Rh status on OS and PFS specifically in patients with HR+ HER2- mBC treated with CdK4/6 inhibitors. As far as we know, this is the first study to explore the influence of ABO/Rh blood groups as an easily accessible prognostic factor in patients with HR+/HER2- mBC receiving CdK4/6i treatment. Thus, it stands as an original contribution to the field. However, additional studies involving larger patient cohorts need to confirm our findings.

Disclosures

Ethics Committee Approval: All procedures conducted in this study involving human participants complied with the ethical standards of the institutional and national research committee, in addition to the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical norms. The Ethics/Institutional Review Board of the Kartal Dr. Lütfi Kirdar City Hospital, Istanbul, Turkey, approved the research - Approval Number: 2023/514/250/2, 29.05.2023.

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