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Original article

Effect of ABO blood type on the outcomes of patients with metastatic renal cell carcinoma treated with first-line tyrosine kinase inhibitors

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Abstract

Objectives: To assess the effect of blood type on survival outcomes and adverse events (AEs) in patients treated with tyrosine kinase inhibitors (TKIs) for metastatic renal cell carcinoma (mRCC).

Materials and methods: Patients who received TKIs as first-line therapy for mRCC between 2008 and 2015 at our hospital were included in the study ($n = 136$). Patients were divided into 2 groups based on their blood type as O and non-O. Survival outcomes and AEs were compared according to blood type. Cox regression models were used for univariate and multivariate survival analyses.

Results: Of the 136 patients, 34 (25%) and 102 (75%) had O and non-O blood types, respectively. Blood type O was associated with an increased number of disease sites. There were no differences between the 2 groups with respect to other baseline characteristics. The progression-free survival in patients with O and non-O blood types was 12.1 and 11.6 months, respectively; the overall survival was 34.4 and 24.8 months, respectively. On univariate and multivariate analyses, the ABO blood type was not a significant prognostic factor for progression-free survival or overall survival. Furthermore, the incidences of serious AEs were similar in the 2 blood groups.

Conclusions: ABO blood type was not associated with survival outcomes or incidences of serious AEs in mRCC patients treated with TKIs. However, blood type O may be associated with an increased number of disease sites. © 2017 Published by Elsevier Inc.

Keywords: ABO blood group system; Adverse drug event; Renal cell carcinoma; Treatment outcome; Survival; Targeted molecular therapy

1. Introduction

The ABO blood grouping system was the first genetic polymorphism discovered in humans [1]. ABO blood group antigens are expressed not only on the surfaces of erythrocytes but also on a large number of human cells and tissues, including epithelia, sensory neurons, platelets, and the vascular endothelia [2]. Since their discovery in 1900, blood groups have been studied in the context of many chronic diseases, including cardiovascular and infectious conditions [3–5]. A number of epidemiological studies have also assessed the associations between ABO blood type and cancer [6]. Some of the most consistently observed associations include the link between non-O blood types and pancreatic cancer, which was also confirmed in a genome-wide association study [7]; and between non-O blood types (particularly blood type A) and gastric cancer [8] as well as atrophic gastritis [9].

Such associations remain controversial in patients with renal cell carcinoma (RCC), although blood type antigens are also expressed on the surfaces of kidneys and RCC lines [10]. In a recent study of 900 patients who underwent surgery for locoregional RCC, non-O blood type was identified as an independent predictor of mortality [11]. Another study revealed blood type O to be associated with the absence of lymph node metastasis, but not necessarily with a more favorable prognosis [12]. In a more recent

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study conducted in 3,172 patients with RCC, no significant association was observed between ABO blood type and prognosis [13]. Moreover, much less information has been published on blood type association with metastasis in patients who were not eligible for surgery, as most studies were conducted only in patients who underwent surgical treatment.

An improved understanding of the biology and pathogenesis of RCC has led to the development of molecular targeted therapies. Among these, tyrosine kinase inhibitors (TKIs) have largely supplanted cytokine-based therapies and become the standard first-line treatment for metastatic RCC (mRCC), leading to improved disease prognosis. Previous studies, however, have demonstrated that resistance to first-line TKIs develops within 6 to 11 months in most patients with mRCC [14,15]. A recent study suggested that CD44 induced by tumor necrosis factor-α had a significant role in resistance to sunitinib, one of the common TKIs used for mRCC [16]. Polymorphisms at the ABO gene locus are reportedly associated with circulating levels of tumor necrosis factor-α [17].

Thus, there are sufficient data to suggest a possible role for ABO blood type in the outcomes of patients with mRCC who are treated with TKIs. Therefore, this study aimed to assess the effect of ABO blood type on survival outcomes in patients treated with TKIs as first-line therapy for mRCC. We specifically compared those with blood type O to those with non-O blood types based on the aforementioned studies that suggested that the O blood type was uniquely associated with survival outcomes [11,12]. Furthermore, we evaluated the association between ABO blood type and the risk of serious adverse events (AEs) in these patients.

2. Material and methods

2.1. Patients

The Internal Ethics Review Board of Tokyo Women's Medical University approved this retrospective study, which was performed in accordance with the tenets of the Declaration of Helsinki (registered approval number: 4014). The medical record archives of patients treated between 2008 and 2015 at our department were, retrospectively, reviewed. During this period, 162 patients received a TKI (including sunitinib, sorafenib, or pazopanib) as a first-line therapy for mRCC. Patients with a history of undergoing prior cytokine therapies or had insufficient data were excluded; ultimately, 136 patients were available for analysis. The median follow-up time for all cohorts was 18 months (interquartile range: 10–30 months).

2.2. TKI treatment and toxicity assessment

At our department, patients normally commenced sunitinib treatment with 50 mg orally once daily in 6-week cycles according to a 4-week-on/2-week-off treatment schedule, or in 3-week cycles based on a 2-week-on/1-week-off treatment schedule, as described by Kondo et al. [18]. Sorafenib was administered at 400 mg twice daily and pazopanib was administered at 800 mg once daily. Doses were modified based on the guidelines of each therapy [19–21]. Treatment with these agents continued until disease progression or the development of intolerable AEs.

All patients underwent baseline evaluation, including tumor imaging and chest computed tomography, before treatment, and was then followed at least once a month during treatment. Objective clinical responses were assessed based on the Response Evaluation Criteria in Solid Tumors version 1.1 guidelines using computed tomography every 2 to 3 months. AEs were graded according to the National Cancer Institute's Common Terminology Criteria for AEs, version 4.0. Histologic tumor types were categorized according to the World Health Organization's 2004 classification.

2.3. Statistical analysis

Patients were divided into 2 groups based on their blood type as O and non-O. The Fisher exact test, chi-square test, Student *t*-test, and Mann-Whitney *U* test were performed to compare each variable between the 2 groups, as appropriate. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared using the log-rank test. PFS was defined as the interval between first-line TKI therapy initiation and the date of progression or death from any cause, whichever occurred first. OS was defined as the interval between first-line TKI therapy initiation and death from any cause. The following clinicopathological characteristics (which were derived from data produced in previous studies) were assessed for a possible association with survival outcomes using multivariate Cox proportional hazards regression models: the Memorial Sloan-Kettering Cancer Center (MSKCC) risk, histologic subtype, number of disease sites, pretreatment serum C-reactive protein (CRP) level, targeted agent of choice for first-line therapy, and ABO blood type [22–24]. A difference was considered significant when $P < 0.05$. Significance was calculated using the JMP 11.0.0 software (SAS institute, Cary, NC).

3. Results

3.1. Patient characteristics

The baseline demographic and clinical characteristics of the patients are listed in Table 1. Of the 136 patients, 34 (25%) and 102 (75%) had O and non-O blood types, respectively. Patients with blood type O had 2 or more disease sites significantly more frequently compared with those with non-O blood types (68% vs. 52%, respectively; $P = 0.045$). There was no significant difference between the blood groups in terms of age, sex, MSKCC risk,