Pretreatment absolute monocyte count is a novel biomarker for predicting worse clinical outcome in chemo-resistant urothelial carcinoma patients treated with pembrolizumab

Koichiro Ogihara[1], Eiji Kikuchi[2], Takashi Okabe[3], Seiya Hattori[4], Ryo Yamashita[5], Syunsuke Yoshimine[6], Suguru Shirotake[3], Kazuhiro Matsumoto[1], Ryuto Nakazawa[2], Ryuichi Mizuno[1], Satoshi Hara[4], Masafumi Oyama[3], Takeshi Masuda[6], Masashi Niwakawa[5], and Mototsugu Oya[1]

1: Dept. of Urology, Keio University School of Medicine, Tokyo, Japan 2: Dept. of Urology, St. Mariannna University School of Medicine, Kanagawa, Japan 3: Dept. of Uro-Oncology, Saitama Medical University International Medical Center, Saitama, Japan 4: Dept. of Urology, Kawasaki Municipal Hospital, Kanagawa, Japan 5: Dept. of Urology, Shizuoka Cancer Center, Shizuoka, Japan 6: Dept. of Urology, Saitama City Hospital, Saitama, Japan

Introduction

- Immune checkpoint inhibition is a novel approach for cancer therapy that has advanced treatment options in chemo-resistant urothelial carcinoma (UC).
- However, there is still no reliable biomarker is available for predicting worse clinical outcome in chemo-resistant UC patients treated with pembrolizumab.
- We focused on absolute monocyte count (AMC) that is reported to modulate immune response in the tumor microenvironment and a possible biomarker for predicting prognosis in various malignancies.
- Previous studies reported that high AMC reflected high tumor-associated macrophages, which promoted tumorigenesis and tumor progression.

Purpose

To evaluate whether high pretreatment AMC (pre-AMC) could predict subsequent clinical outcomes in chemo-resistant UC patients treated with pembrolizumab.

Materials and Methods

- From December 2017 to April 2019, we retrospectively reviewed 93 patients who were treated with pembrolizumab for chemo-resistant UC at our 5 institutions.
- 3 patients who had a short observation period (less than 2 months) was excluded. After the exclusion of the patient, the remaining **90** patients were assessed in the present study.
- The mean age was 72.4 years, the mean follow-up period was 6.73 months, and the mean number of pembrolizumab administration was 5.67.
- Diagnostic imaging including computed tomography of the chest/abdomen/pelvis with or without intravenous contrast was performed every 2-3 courses of pembrolizumab.
- We defined patients with AMC of **>342** as the high pre-AMC group according to a calculation by receiver-operating curve analysis.

Results

Table 1: Patient background

n (%)	High pre-AMC group (n=53)	Low pre-AMC group (n=37)	p value
Sex			0.278
Male	40 (75.5)	25 (67.6)	
Female	13 (24.5)	12 (32.4)	
Mean age (years)	71.3±9.91	73.2±8.61	0.495
Mean progression-free duration (months)	16.0±40.0	12.1±12.0	0.607
Performance Status			0.199
0 or 1	50 (94.3)	37 (100)	
2	3 (5.7)	0 (0)	
Smoking history			0.544
Yes	28 (52.8)	20 (54.1)	
No	23 (43.4)	17 (45.9)	
Unknown	2 (3.8)	0 (8.2)	
Primary lesion of main tumor			
Pelvis	11 (20.8)	7 (18.9)	
Ureter	10 (18.8)	11 (29.7)	
Bladder	32 (60.4)	19 (51.4)	
Radical operation for primary tumor			0.198
Yes	36 (67.9)	29 (75.7)	
No	17 (32.1)	8 (54.3)	
Liver metastasis			0.09
Yes	9 (17.0)	2 (5.4)	
No	44 (83.0)	35 (94.6)	
Adverse events (Grade 3 or 4)			0.172
Yes	10 (18.8)	11 (29.7)	
No	43 (81.2)	26 (70.3)	
Number of chemotherapy			0.338
≤5 courses	35 (66.0)	22 (59.5)	
6 courses≤	18 (34.0)	15 (40.5)	
Salvage chemotherapy			0.02
Administered	42 (79.2)	21 (56.8)	
Not administered	11 (20.8)	16 (43.2)	

Table 2: The association between pre-AMC and response to pembrolizumab by RECIST ver 1.1

	CR・PR・SD group (n=39)	PD group (n=51)	p value
Pre-AMC	387±2425	495±292	**0.055**

Table 2: Pre-AMC in PD group was higher than that in CR・PR・SD group. However, there was no significant differences between two proups.

Figure 1. Progression-free survival and cancer-specific survival according to pre-AMC

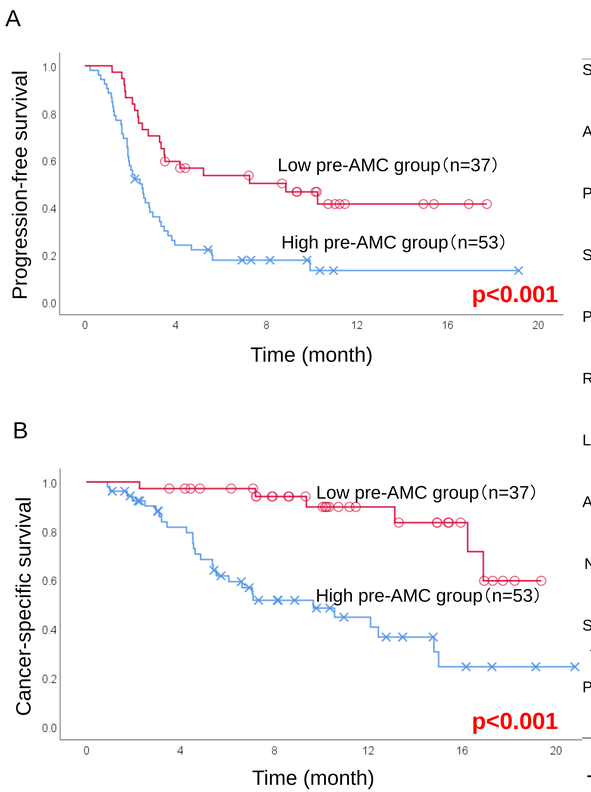

Figure 1: A Kaplan-Meier curve of progression-free survival (PFS) (A) and cancer-specific survival (CSS) (B) in chemo-resistant urothelial carcinoma patients treated with pembrolizumab.

Table 3. Cox regression analysis for progression and cancer-specific death

	Progression			Cancer-specific death		
	Univariate p value	Multivariate HR (95% CI)	p value	Univariate p value	Multivariate HR (95% CI)	p value
Sex	0.499			0.065		
Male						
Female						
Age	0.535			0.437		
<70 years						
70 years≤						
Performance status	0.718			0.334		
0 or 1						
2						
Smoking history	0.215			0.728		
Yes						
No						
Primary lesion of the main tumor	0.959			0.051		
Upper tract						
Bladder						
Radical operation for primary tumor	0.795			0.286		
Yes						
No						
Liver metastases	***0.01***		***0.028***	0.67		
Yes		2.25 (1.16-4.38)				
No		1				
Adverse events (Grade 3 or 4)	0.166			0.1		
Yes						
No						
Number of chemotherapy	0.081			0.071		
≤5 courses						
6 courses≤						
Salvage chemotherapy	0.517			0.138		
Administered						
Not administered						
Pre-AMC	***<0.001***		***0.007***	***<0.001***		***<0.001***
<342		1			1	
342≤		2.38 (1.09-5.18)			8.4 (1.04-66.7)	

Table 3: Multivariate Cox regression analysis revealed that pre-AMC level of >342 (p=0.007), and liver metastases (p=0.028) were the independent indicators for disease progression. Furthermore, pre-AMC level of >342 was the only independent indicators for cancer-specific death (p<0.001).

Conclusion

Elevated pre-AMC could identify a population with a poor response to pembrolizumab treatment among chemo-resistant UC patients.

COI disclosure information

First author: Koichiro Ogihara

The authors have no financial conflicts of interest to disclose concerning the presentation.