CLINICAL OUTCOME OF PEMBROLIZUMAB FOR VARIOUS MALIGNANCIES IN SINGLE INSTITUTE IN VIETNAM

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ABSTRACT

***Background**: Pembolizumabis an immune check-point inhibitor to be targeted for Programmed cell death 1 (PD-1). It has been shown promising efficacy to various types of cancer. In Vietnam, pembrolizumab has been available since early of 2018. We has performed to treat certain types of cancer with pembrolizumabby now, herein we report the early experience with pembrolizumabin single institute in Vietnam.*

***Methods**: From 1st January 2018 to 31st October 2018, total 19 patients was treated with pembrolizumab. Among 19 patients, 12 patients were evaluable and we analyzed their clinical outcomes, and response was determined by RECIST criteria version 1.1.*

***Results**: Among 12 evaluable patients, males are 4 and female are 8; and median age was 61 years (range, 34~76). Most common disease was lung cancer (n=6) and others are gastric cancer (n=2), head and neck cancer, colon cancer, lymphoma and melanoma (each n=1). Every patients were stage IV or relapsed status, and 11 of 12 patients had been treated with at least one kind of chemotherapy before pembrolizumab. Response rate of total patients was 58.3%(7/12) [complete remission: 16.7% (2/12), partial response: 41.7%(5/12)]. Stable disease was 8.3%(1/12), and progressive disease was 33.3%(4/12). Disease control rate was 66.7%(8/12). Median progression free survival was 7.2 months (range, 0~15.6). Median overall survival was not reached. Among responders (n=8),most of them (7/8) showed the response within 3 cycles of pembrolizumab. Serious adverse event was not found except one patients who experienced grade 2 dermatomyositis, which are improved by steroid treatment and withdrawal of pembrolizumab.*

***Conclusion**: According to our early experience in Vietnam with pembrolizumab, the clinical outcome was promising and comparable to global data.Long term follow-up and more patient's enrollment to analyze the efficacy and toxicity of pembrolizumab are required.*

I. INTRODUCTION

The successful development of therapeutic agents targeting the PD-1/PD-L1 (programmed cell death-1/programmed cell death-ligand 1) axis has been a major therapeutic advancement in oncology. Pembrolizumab is the first anti–PD-1 agent to be approved by the US Food and Drug Administration (FDA). Pembrolizumab was also approved for use in melanoma in Australia, Israel, Korea, Macau, and the United Arab Emirates and was recently recommended for approval in the European Union [1].

From the early of 2018, pembrolizumab was also approved in Vietnam, and our institute started to use pembroizumab for various malignancies. Herein, we reported the clinical outcomes of the patients treated with pembrolizumab in our single institute.

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II. METHODS

From 1st January 2018 to 31st October 2018, total 19 patients were treated with pembrolizumab in our institute. Among 19 patients, 7 patients were not evaluable because of follow-up loss or early death without response evaluation. Therefore, 12 patients were analyzed for the clinical outcomes and toxicities retrospectively. Two of them had started to be give pembrolizumab before our institute. Including them, median follow-up duration for pembrolizumab is 7.9 months (range, 2.7~20.5).

Response evaluation was determined by RECIST criteria version 1.1., and survival analysis for overall survival and progression free survival were done by Kaplan-Meier survival analysis.

III. RESULTS

Among 12 evaluable patients, males are 4 and female are 8; and median age was 61 years (range, 34~76). Most common disease was lung cancer (n=6) and others are gastric cancer (n=2), head and neck cancer, colon cancer, lymphoma and melanoma (each n=1). Every patients were stage IV or relapsed status. Two patient were given with pembrolizumab as a first-line chemotherapy for stage IV lung cancer and melanoma. Other patients had been treated at least one kind of chemotherapy (median 1.5, range 0~4) and 5 patients had been treated with radiation before pembrolizumab. Ten patients were checked for PD-L1 expression and/or microsatellite instability (MSI) status before pembrolizumab, and all of them were positive for these test [PD-L1 (+), n=9; MSI-high, n=1].

Response rate of total patients was 58.3% (7/12) [complete remission: 16.7% (2/12), partial response: 41.7% (5/12)]. Stable disease was 8.3%(1/12), and progressive disease was 33.3%(4/12). Disease control rate was 66.7% (8/12). Median progression free survival was 7.2 months (range, 0~15.6). (figure 1) No one died during follow-up period, therefore median overall survival was not reached. Among responders (n=8), most of them (7/8) showed the response within 3 cycles of pembrolizumab. Basic characteristics and clinical outcome was shown in Table 1.

Serious adverse event was not found except one patients who experienced grade 2 dermatomyositis, which was improved by steroid treatment and withdrawal of pembrolizumab.

IV. DISCUSSION

Anti-tumor activity of pembrolizumab to malignancy is various according to histology and molecular genetic properties. In advanced lung cancer patients, the response rate for non-small cell lung cancer among PD-L1 positive was around 45% and small cell lung cancer was about 33% [2-3]. In our study, 3 of 6 (50%) of lung cancer patients showed partial response. In gastric cancer patients, response rate with pembrolizumab was 15%, and our study showed 1 of partial response and 1 of stable disease [4]. In head and neck cancer, response rate with pembrolizumab was about 18% and our one patient showed progression within 3 months. [5] In melanoma patients, response rate with pembrolizumab was about 22% and our one patient showed partial response [6]. Especially, two patients with extranodal NK/T cell lymphoma (ENKTL) and relapsed colon cancer patients showed complete remission. In ENKTL patients, there are limited number of studies and response rate seems to be about 50% [7-8]. In colon cancer study, response rate was about 40% [9].

Adverse event was generally tolerable for all patients except one patient who experienced grade 2 dermatomyositis. The patient was treated with steroid and stopped pembrolizumab, and then the skin rash, weakness, and elevated muscle enzymes were improved [10].

V. CONCLUSIONS

According to our early experience in Vietnam with pembrolizumab, the clinical outcome was promising and comparable to global data. Long term follow-up and more patient's enrollment to analyze the efficacy and toxicity of pembrolizumab are required.

REFERENCE

1. Khoja L, Butler MO, Kang SP, Ebbinghaus S, Joshua AM. Pembrolizumab. J Immunother Cancer. 2015 Aug 18;3:36.
2. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR; KEYNOTE-024 Investigators. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Nov 10; 375(19):1823-1833.
3. Ott PA, Elez E, Hiret S, Kim DW, Morosky A, Saraf S, Piperdi B, Mehnert JM. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. J ClinOncol. 2017 Dec 1;35(34):3823-3829.
4. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, Sun W, Jalal SI, Shah MA, Metges JP, Garrido M, Golan T, Mandala M, Wainberg ZA, Catenacci DV, Ohtsu A, Shitara K, Geva R, Bleeker J, Ko AH, Ku G, Philip P, Enzinger PC, Bang YJ, Levitan D, Wang J, Rosales M, Dalal RP, Yoon HH. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. JAMA Oncol. 2018 May 10;4(5):e180013.
5. Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, Heath K, McClanahan T, Lunceford J, Gause C, Cheng JD, Chow LQ. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol. 2016 Jul;17(7):956-965.
6. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A; KEYNOTE-006 investigators. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N EnglJ Med. 2015 Jun 25;372(26):2521-32.
7. Haverkos BM, Coleman C, Gru AA, Pan Z, Brammer J, Rochford R, Mishra A, Oakes CC, Baiocchi RA, Freud AG, Porcu P. Emerging insights on the pathogenesis and treatment of extranodal NK/T cell lymphomas (ENKTL). Discov Med. 2017 Mar;23(126):189-199.
8. Li X, Cheng Y, Zhang M, Yan J, Li L, Fu X, Zhang X, Chang Y, Sun Z, Yu H, Zhang L, Wang X, Wu J, Li Z, Nan F, Tian L, Li W, Young KH. Activity of pembrolizumab in relapsed/refractory NK/T-cell lymphoma. J HematolOncol. 2018 Jan 31;11(1):15.
9. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA Jr. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015 Jun 25;372(26):2509-20.
10. Liewluck T, Kao JC, Mauermann ML. PD-1 Inhibitor-associated Myopathies: Emerging Immune-mediated Myopathies. J Immunother. 2018 May;41(4):208-211.

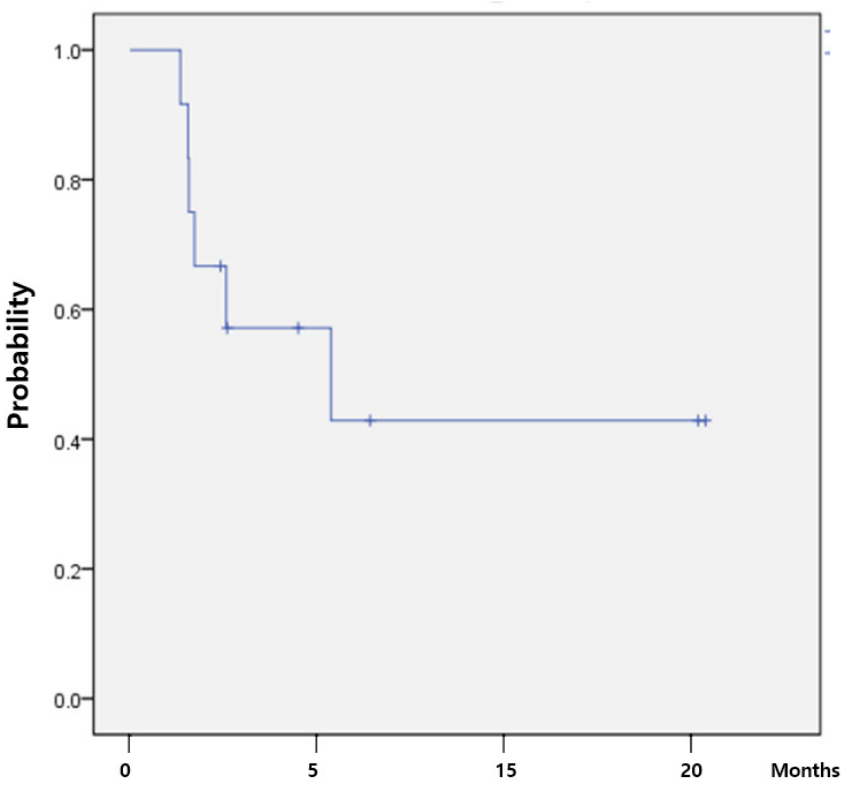

Figure 1. Progression free survival.

Median progression free survival was 7.2 months (range, 0~15.6)

Table 1. Basic characteristics and clinical outcomes of the patients

No.	Sex/Age	Diagnosis	PD-L1 (%)	MSI	Response	Response cycle	PFI (month)	Survival (month)
1	F/71	Lung	20	ND	PD		2.3	9.8
2	M/68	Lung	55	ND	PD		2.1	7.7
3	F/55	Lung	20	ND	PD		2.1	3.9
4	M/64	Lung	ND	ND	PR	3	8.6	8.6
5	M/60	Lung	60	ND	PR	3	6.0	9.2
6	M/53	Lung	90	ND	PR	3	7.2	8.1
7	F/59	Stomach	21	Low	SD	4	3.5	3.5
8	F/69	Stomach	40	ND	PR	3	3.2	3.2
9	M/76	H&N	ND	ND	PD		1.8	2.7
10	F/44	Melanoma	70	ND	PR	3	3.4	3.7
11	F/34	Lymphoma	60	ND	CR	3	20.3	20.3
12	F/61	Colon	ND	High	CR	6	20.5	20.5

Abbreviation: H&N, head and neck; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; PFI, progression-free interval; ND, not done