Issues identified after the establishment of the irAE task team

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Introduction

In May 2018, our hospital formed an immune-related adverse events (irAEs) task team, which includes an outpatient pharmacist office, for the early detection and treatment of irAEs. The following activities are conducted in the hospital: the creation of monitoring reports using protocol-based pharmacotherapy management, the unification of laboratory tests, the creation of outpatient triage sheets, the creation of a HBV reactivation prevention system, the revision of hospital standards, the sharing of irAE cases at cancer chemotherapy committee meetings, reporting to the Pharmaceuticals and Medical Devices Agency (PMDA), and in-hospital workshops. Specific interventions by pharmacists include screening and drug guidance prior to administration at the time of initial induction, and the monitoring of adverse events at every second induction and thereafter. However, there have been a number of serious cases since then, and the contribution of pharmacists remains unclear. In the present study, we investigated the challenges of pharmacist work through the irAE cases at our hospital that led to the PMDA report.

Methods

The PMDA report included patients diagnosed with cancer between January 2021 and April 2024 who received the following drugs as single agents or in combination: nivolumab (nivo), pembrolizumab (pembro), atezolizumab (ate), durvalumab (dur), avelumab (ave), tremelimumab (tre), and ipilimumab (ipi).

The, carcinoma, drug, adverse event, survey items included age, sex, departmentseverity of the adverse event, presence of a pharmacist intervention, details on pharmacist suggestions, circumstances at the time of occurrence of the irAE, and multiple irAE complications and outcomes.

The study period for the relationship between the occurrence of irAEs and the prognosis of patients treated with ate+bev for unresectable liver cancer was the same. Survey items included sex, age, the Child-Pugh classification, history of hepatitis, time of initiation, efficacy, and concomitant medications (oral proton pump inhibitors (PPIs) or oral antibiotics). Of the adverse events that occurred during the study period, irAEs were those that were judged to be causally related to ICIs by the physicians in charge of the patients. The severity of irAEs was evaluated based on the Common Terminology Criteria for Adverse Events ver. 5.0, and irAE occurrence was defined as any grade (Grade:G).

Statistical analyses were performed using SPSS ver.27 (SPSS, Inc.,Tokyo, Japan). Patient backgrounds were compared between the irAE group and the non-irAE group. Differences between the two groups were compared by the Mann-Whitney U test and χ2 test. Survival was compared by the Kaplan-Meier method. The Log-rank test was used for intergroup comparisons, and a significance level <5% was considered to be significant.

This study was conducted after approval by the Research Ethics Committee of the Corporate Hospital Group, Hitachi Ltd. (Approval No.2018-67).

Results

Table 1. Backgrounds of patients reported to PMDA

	n=59
Age (range)	72 (43-86)
Sex male/female (%)	48/11 (81.4/18.6)
Medical department Gastroenterology/Urology/Pulmonary/Respiratory/ Breast/Gynecology	26/16/14/2/1 (44.1/27.1/23.7/3.4/1.7)
Carcinoma Lung/renal/esophageal/stomach/liver/bladder/colon/ bile duct/breast/uterine	14/11/8/7/7/5/2/2/2/1 (23.7/18.6/13.6/11.9/11.9/8.5/3.4/3.4/3.4/1.7)
By drug nivo/pembro/ate+bev/nivo+ipi/ate/dur+tre/ave/nivo+cabo/dur	20/19/6/5/3/2/2/1/1 (33.9/32.2/10.2/8.5/5.1/3.4/3.4/1.7/1.7)
Adverse events for all grades Colitis/hepatotoxicity/pneumonia/hypoadrenalism/ hypothyroidism/skin disorders/hypopituitarism/gastroenteritis/ IR/pancreatitis/cholangitis/renal disorders/arthritis/type I diabetes/encephalitis/iris ciliary body inflammation/ myasthenia gravis/thrombocytopenia/myositis/psoriasis/PMR	14/8/7/6/6/5/4/3/3/ 2/2/2/2/2/1/1/1/1/1/1/1 (19.2/11.0/9.6/8.2/8.2/6.8/5.5/4.1/4.1 2.7/2.7/2.7/2.7/2.7/1.4/1.4/1.4/1.4/1.4/1.4/1.4)
By Grade -1/2/3/4/5	2/1/24/29/2/1 (3.4/1.7/40.7/49.2/3.4/1.7)
Grade 3 or higher adverse events. Colitis/hepatotoxicity/pneumonia/skin isorders/gastroenteritis/ hypoadrenalism/type I diabetes/renal disorders/IR/PMR/ hypothyroidism/arthritis/myositis/thrombocytopenia/ myasthenia gravis/encephalitis/pancreatitis	6/6/4/3/3/3/2/ 1/1/1/1/1/1/1/1/1/1/1 (16.2/16.2/10.8/8.1/8.1/8.1/5.4/ 2.7/2.7/2.7/2.7/2.7/2.7/2.7/2.7/2.7/2.7/2.7)
Severity Non-serious/serious	16/43 (27.1/72.9)
Pharmacist immediate intervention No/Yes	24/35 (40.7/59.3)
Contents of the immediate intervention by the pharmacist Drug withdrawal/prescribing/other department consulting/drug withdrawal/ prescribing/other department consulting/ prescribing/ other/prescribing/other/ prescribing/ testing/ other department consulting/other department consulting	9/6/5/5/4/3/2/1 (25.7/17.1/14.3/14.3/11.4/8.6/5.7/2.9)
Situation at the time of irAE manifestation Regular visits/Coming to the hospital by oneself/during hospitalization	34/16/9 (57.6/27.1/15.3)
Multiple irAE complications 3/2/1	3/8/48 (5.1/13.6/81.4)
Outcome Recovery/slight recovery/death	53/4/2 (89.8/6.8/3.4)

Table 2. Example of response after irAE manifestation

irAEs	G	Situation at the time of irAE manifestation	irAE Expression status	Intervention by pharmacists	Medical treatment	Out come	Post-onset course
Hypoadrenal function	3	Coming to the hospital by oneself	Loss of appetite, persistent fatigue	Yes	Cortisol replacement	recovery	Continuation
Hypo-thyroidism	2	Regular visits	Tests at regular visits. TSH:29.4, FT4:0.77	Yes	Thyroid hormone replacement	alleviated	Continuation
Skin disorders	3	Regular visits	Generalized Erythema	Yes	Topical steroids	alleviated	Continuation
Colitis	3	Regular visits	BS4-6 3-4 times/day, bloody stools	Yes	Steroids i.v. →Oral	recovery	Withdrawal → Resumption
Liver damage	3	Regular visits	Laboratory tests at periodic visits AST(G3)/ALT(G3)	Yes	Steroids i.v. →Oral	recovery	Withdrawal → Resumption
Pneumonia	3	Coming to the hospital by oneself	Fever, shortness of breath	Yes	Steroid pulse →Oral	recovery	Dosing discontinuation
Kidney damage	3	Regular visits	urinary protein 3+, CRE(G2),edema(G1)	Yes	Steroids →Oral	recovery	Dosing discontinuation

Table 3. Background of patients who received ate+bev therapy

Resection is not possible for hepatocellular carcinoma	total n=43	irAE group n=36	non-irAE group n=7	p
Median Age (Range)	77 (57-89)	78 (58-89)	75 (57-86)	0.429
Sex Male/Female	39/4 (90.7/9.3)	33/3 (91.7/8.3)	6/1 (85.7/14.3)	0.523
Age Older than 75/Younger than 75	29/14 (67.4/32.6)	25/11 (69.4/30.6)	4/3 (57.1/42.9)	0.410
Child-Pugh Classification A/B	39/4 (90.7/9.3)	33/3 (91.7/8.3)	6/1 (85.7/14.3)	0.523
Hepatitis HBV/HCV/NBNC	2/17/24 (4.7/39.5/55.8)	2/14/20 (5.6/38.9/55.6)	0/3/4 (0.0/42.9/57.1)	0.539
Dosing start date 1st/2nd	31/12 (72.1/27.9)	26/10 (72.2/27.8)	5/2 (71.4/28.6)	0.644
Efficacy mRECIST PD/non-PD	13/30 (30.2/69.8)	11/25 (30.6/69.4)	2/5 (28.6/71.4)	0.648
Concomitant medications Oral PPIs/antibiotics/none	23/0/20 (53.5/0/46.5)	20/0/16 (55.6/0/44.4)	3/0/4 (42.9/0/57.1)	0.418

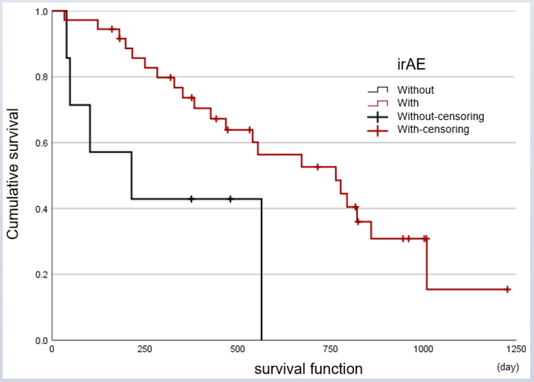

Figure 1. Relationships between irAEs and OS after ate+bev treatment for inoperable hepatocellular carcinoma

Discussion

The irAE rate of G3 or higher by pembro was previously reported to be 14.3% (817/5,707 cases) for monotherapy and 26.0% (1,692/6,503 cases) for combination therapy[1)]. Although a simple comparison is not possible in the present study, these rates were 8.8% of monotherapy cases (7/80 cases) and 9.4% of combination therapy cases (5/53 cases) at our hospital, indicating that in-hospital maintenance efforts undertaken by the irAE task team were effective. In addition, 82.9% (29/35) of patients who received an immediate intervention by the pharmacist recovered from their symptoms, suggesting that the pharmacist played a role in team medicine.

Among adverse events, colitis was the most common, followed by liver injury and pulmonary inflammation. The reported mechanisms of irAEs include T cell activation against normal tissues, the induction of inflammatory cytokines, increased autoantibody production, and damage by anti-CTLA-4 antibodies[2)] . irAEs also frequently occur in the skin, gastrointestinal tract, liver, and endocrine tract. The majority of skin disorders are mild G1-2. Endocrine disorders may be controlled by replacement therapy[3)].

In unresectable hepatocellular carcinoma cases that received ate+bev, median survival was slightly longer in the irAE group than in the non-irAE group （p=0.002）. The incidence of irAEs in the present study, for which a causal relationship cannot be ruled out, differed from the values reported by Fukushima[4)] and D'Alessio[5)] (21.3 and 71%, respectively). However, the incidence of irAEs in the present study was 83.7%, which is consistent with longer OS in the irAE group. irAEs in IMbrave150 with undeniable causality was 83.9%[6)], which is in accordance with the present results. If irAEs are a favorable prognostic factor for ICI treatment, they must be managed correctly. As reported by Medina et al[7)], the pharmacist's role must be fulfilled, including knowledge of irAEs, monitoring and management of adverse events, and patient education.

Conclusion

While ICIs are expected to be effective, they are also associated with serious irAEs. A system for the early detection of irAEs and the provision of safe cancer drug therapy is needed. Since symptoms were relieved by an immediate intervention by a pharmacist in 82.9% (29/35) of patients, the pharmacist plays a role in team medicine. In addition, the inauguration of the task team for irAE measures will promote the appropriate use of ICIs. On the other hand, the development of countermeasures against combined immunotherapy and cross-organ use is an issue that needs to be addressed.

References

1) Guide for appropriate use of *KEYTRUDA*®2024 2) PMID:29320654
3) PMID:34724392 4) PMID:37023703 5) PMID:35313048
6) PMID:32402160 7) PMID:31694455

I have no COI with regard to our presentation.

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