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ORIGINAL RESEARCH ARTICLE

Initiatives for immune-related adverse events by the outpatient pharmacist clinic

Kiyonori Hamatake, Kazuaki Kojima*

Department of Pharmacy, Takatsuki Red Cross Hospital, 1-1-1 Abuno, Takatsuki, Osaka 569-1096, Japan. E-mail: k-kojima@takatsuki.jrc.or.jp

ABSTRACT

Early detection is the key in managing side effects because immune-related adverse events (irAEs) are becoming more serious, and their onset time differs. In our hospital, we conducted an outpatient pharmacist clinic for early detection of irAEs by self-care practice for the cases of immune checkpoint inhibitor administration. As a result of a retrospective survey of 207 cases, the percentage of irAEs found by pharmacist's suggestion of the outpatient pharmacist clinic increased over time, and a high detection ratio was obtained even for irAEs with a late onset time. The incidence of serious irAEs was higher than that in the immediate post-marketing surveillance, and different factors were considered. Although there were some problems, the outpatient pharmacist clinic had a certain effect.

Keywords: Immune Checkpoint Inhibitors; Immune Combination Therapies; Immune-related Adverse Events; Outpatient Pharmacist Clinic; Clinical Pathway

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1. Introduction

Since the introduction of immune checkpoint inhibitors (ICIs), their use has continued to grow[1]. Immune combination therapies using two types of ICIs have also appeared, and further use of ICIs is expected as the number of applicable cancer types expands[2-4]. ICIs have immune-related adverse events (irAEs) as a side effect to be noted[5]. IrAEs possess characteristics that differ from the adverse events of conventional cytotoxic anticancer drugs and are difficult to understand because of their wide range of adverse events. The onset time of the irAE varies, and the discovery by patients' self-observation is the key to side effect management[6-9]. Additionally, the incidence of the irAE is said to be higher with immune combination therapies, so further attention is required.

At our hospital, we provide the outpatient pharmacist clinic, including patient education, aiming at the early detection of the irAE through self-care practice. We report on the administration of ICI treatment at our hospital and the current status of the outpatient pharmacist clinic.

2. Methods

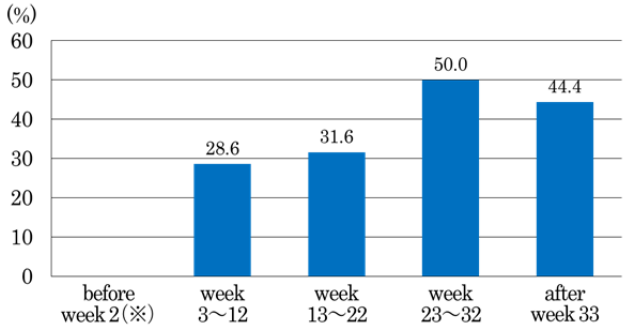
In implementing ICIs, we established a system that enables close cooperation with each clinical department. When irAEs were suspected in a patient receiving ICIs, a briefing session was held to gain understanding so that medical examinations of other departments could pro-

ceed smoothly. By setting laboratory test items specialized for the irAE screening in addition to standardizing them when registering a regimen; it is possible to check the side effect status without omis-omission. An emergency manual for ICI-administered patients was also prepared, and necessary tests were set to prevent individual differences in the initial response. In principle, the first introduction of ICI was conducted in the hospital, and pharmacists intervened before administration to provide patient education for self-care practice, including detailed contents of the irAE and how to fill in the treatment diary. Even after moving to the outpatient clinic, we decided to intervene at the outpatient pharmacist clinic before consulting the doctor, screen irAEs by interview, and provide feedback for the doctor as necessary. These are operated integrally as the ICI clinical pathway. The clinical pathways, tools, and pharmacist's interventions described above contribute to the safe administration of ICI.

We conducted a retrospective medical record survey that focused on the outpatient pharmacist clinic to verify the actual clinical effects of these efforts. The period was set from March 2016 to June 2021. The target patients were those who received ICIs at our hospital. The detection ratio was defined as the percentage of irAEs found by the pharmacist's suggestion of the outpatient pharmacist clinic, and we also investigated the passage of time and the detection ratio for each irAE.

3. Results

Two hundred and seven patients (151 males and 56 females) were treated, and the clinical pathway was used in all cases. The median age was 73.0 years, and the median number of treatment days was 99.0 days.



※ Within week 2, the outpatient pharmacist clinic has not been conducted.

Figure 1. IrAEs detection ratio #1 (n = 78)**.** Detection ratio of irAEs found by pharmacist's suggestion**.**

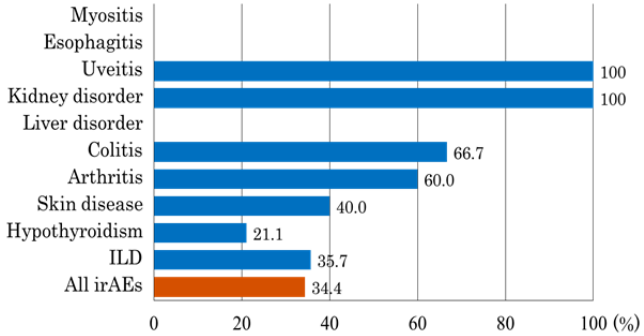


Figure 2. IrAEs detection ratio #2 (n = 64)**.** Detection ratio for each irAE after week 3**.**

irAE Name	Nivolumab (n=69) S	N-S		Pembrolizumab (n=84) S	N-S		Atezolizumab (n=42) S	N-S		Durvalumab (n=12) S	N-S		ALL ICIs (n=207) S	N-S	
Skin disease	2	7	(10.1%)	1	11	(14.3%)					1	(8.3%)	3	19	(10.6%)
Hypothyroidism		6	(8.7%)		11	(13.1%)		3	(7.1%)					20	(9.7%)
ILD	4	2	(8.7%)	5	2	(6.0%)	2		(4.8%)	1	1	(16.7%)	12	5	(8.2%)
Arthritis		1	(1.4%)		2	(2.4%)	1		(2.4%)	1	1	(16.7%)	2	4	(2.9%)
Colitis		1	(1.4%)		3	(3.6%)								4	(1.9%)
Liver disorder		1	(1.4%)	1		(1.2%)		1	(2.4%)				1	2	(1.5%)
Kidney disorder				2		(2.4%)							2		(1.0%)
Uveitis		1	(1.4%)		1	(1.2%)								2	(1.0%)
Esophagitis		1	(1.4%)											1	(0.5%)
Myositis				1		(1.2%)							1		(0.5%)

S: Serious
N-S: Non Serious

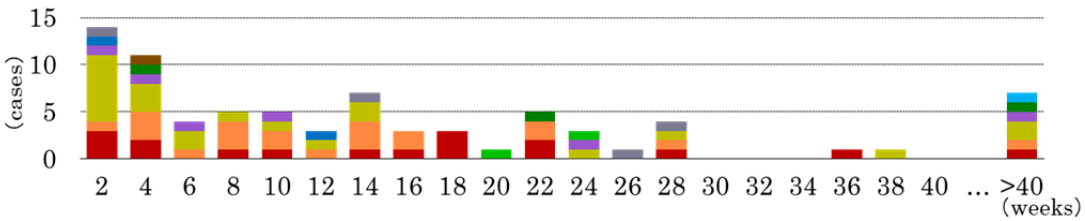


Figure 3. IrAEs report**.** The number of irAEs was 78 out of 207 cases. Skin disease develops relatively early, but other irAEs cannot be timed**.**

The detection ratio increased over time until the 32nd week (**Figure 1**). The detection ratio for each irAE was 100% for kidney disorder and uveitis, followed by over 60% for arthritis and colitis. Conversely, hypothyroidism had the lowest rate at 21.1% (**Figure 2**).

The expression status of the irAE was 78 out of 207 cases. There were 22 cases of skin disease, 20 cases of hypothyroidism, and 17 cases of interstitial lung disease (ILD), which were particularly frequent. ILD tended to become more serious, and skin disease as well as hypothyroidism tended to be mild. The onset time was generally concentrated within 30 weeks, skin disease tended to occur relatively early within 14 weeks, and ILD and hypothyroidism varied (**Figure 3**). The incidence of serious irAEs tended to be higher for all drugs than in the immediate post-marketing surveillance (**Figure 4**). For durvalumab, the difference from the immediate post-marketing surveillance was large.

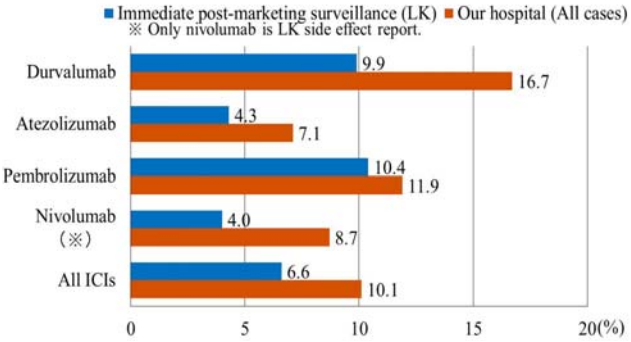


Figure 4. Incidence of serious irAEs. The frequency of occurrence is slightly higher than in general practice**.**

4. Discussion

The detection ratio of irAEs by the outpatient pharmacist clinic increases as the duration of the administration increases, and then, decreases at about 50%. It was considered that irAEs with a late onset time were well detected. Regarding irAEs, which are based on the laboratory test values such as hypothyroidism and liver disorder, there are many cases where the test results are not in time before starting the outpatient pharmacist clinic, and it was considered to be a factor that does not increase the detection ratio. We would like to make it an issue for future system improvement.

The incidence of serious irAEs was generally higher than that in the immediate post-marketing surveillance, which is an index for general medical care, but factors, such as the spread of conventional cytotoxic anticancer drugs combination regimens and immune combination therapies, and the extension of the ICI administration interval were considered to be one of the factors. Durvalumab is mainly used for maintenance therapy after radiotherapy, and the number of cases is small, so we cannot evaluate it at this stage. Moreover, in this survey, we discovered that skin disease occur relatively early, within 14 weeks. We would like to collaborate with nurses in the outpatient chemotherapy room for earlier detection, including early skin care.

5. Conclusion

Supporting patients in multiple occupations is essential for the safe progress of ICI treatment. Although there are some problems, the outpatient pharmacist clinic has a certain effect on the early detection of irAEs by self-care practice.

Conflict of interest

The authors declare no potential conflicts of interest.

Acknowledgements

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