Pharmaceutical Care Contributes to the Advanced Management of Patients Receiving Immune Checkpoint Inhibitors

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Received July 9, 2020; accepted August 30, 2020

We previously reported that successive pharmaceutical care by oncology pharmacy specialists contributes to quality outpatient chemotherapy. However, there are a few reports regarding such care during immune checkpoint inhibitors (ICIs) treatment, despite increasing patients being treated with ICIs and the profile of immune-related adverse events being quite different from that of the adverse effects of cytotoxic agents. We retrospectively evaluated the effectiveness of continuous pharmaceutical care in outpatient ICI treatment, focusing especially on the period of providing pharmaceutical recommendations. The adoption rate, efficacy, and period of pharmaceutical interventions, such as prescription questions and pharmaceutical recommendations, were evaluated. A total of 3597 ICI administrations (366 patients) were evaluated. We performed 2625 face-to-face medication counseling. A total of 282 prescription questions and 147 pharmaceutical recommendations were conducted. Approximately 70% of the questions were regarding ordering of laboratory examination, and 86.5% of these questions were adopted. Pharmaceutical recommendations were categorized into medication recommendations (81.1%), examination recommendations (10.8%), and recommendation of expert consultation (8.1%). The adoption rate of pharmaceutical recommendations was 96.0, and 70% of the medication recommendations attenuated the symptoms. Finally, the provision rate of pharmaceutical recommendations was significantly higher in the first 3 months after ICI treatment initiation. We found that pharmaceutical care contributes to an improved quality of outpatient ICI treatment, and face-to-face pharmaceutical counseling up to 3 months after ICI treatment initiation is the most important.

Key words outpatient chemotherapy; pharmaceutical care; immune checkpoint inhibitor; immune-related adverse event; clinical pharmacy; medical oncology team

INTRODUCTION

Patients suffering from cancer are increasing worldwide. New medication treatments with a variety of action mechanisms have been developed, and their management is becoming complicated and sophisticated. However, outpatient chemotherapy implementation instead of hospitalization is becoming mainstream owing to the advancement of supportive care and enhancement of medical staff with advanced comprehension and experience. Pharmacists assume important roles in the medical care team as drug therapy management representatives. In Japan, pharmaceutical care by face-to-face medication counseling in outpatient chemotherapy is becoming common because of its promotion by the Ministry of Health, Labour and Welfare and the induction of remuneration for such care. There are many reports evaluating pharmacy practice in outpatient chemotherapy, and additional studies are urgently required.

Programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated-4 (CTLA-4) are receptors expressed on the surface of cytotoxic T cells. They interact with their ligands on the cancer cells; the programmed death-ligand 1 in the case of PD-1 and CD80/CD86 in the case CTLA-4. These pathways help them to elude cytotoxic T cell-mediated death. Immune checkpoint inhibitors (ICIs) prevent the binding of receptors and ligands, leading to checkpoint pathway blockage. ICIs have been adopted in a wide range of malignancies such as lung, head and neck, gastric, esophagus, urothelial, and renal cell cancers and melanoma.

Immune-related adverse events (irAEs) occur owing to impaired self-tolerance because of loss of T-cell inhibition, and include broad indications such as dermatologic, gastrointestinal, endocrinal, hepatic, renal, and pulmonary toxicities. The frequency of irAEs is relatively low compared to the adverse effects of cytotoxic agents, and most initial symptoms are manageable. It has also been reported that irAE development is associated with clinical benefit for treatment outcome, and persists after treatment discontinuation. As it is difficult to predict irAE frequency, and as patients sometimes under-report their symptoms and consultation time with physicians is limited, it is necessary to manage irAEs by the medical team. Pharmacists are especially supposed to assume roles such as (1) patient education, (2) patient monitoring, and (3) irAE management, though a few reports suggest that face-to-face pharmaceutical care and laboratory data checking system are useful in irAE management.

We previously reported that successive pharmaceutical care by oncology pharmacy specialists in outpatient chemotherapy contributes to quality implementation of outpatient chemotherapy, although there were few ICI-treated patients. It is important to assess the usability of pharmaceutical care in ICI treatment, and the suitable duration of face-to-face patient care for...
more adequate and efficient pharmacy practice as irAEs usually occur in the relatively early phase of the treatment, and there are increasing number of ICI-treated patients.

In this study, we evaluated the effectiveness of continuous pharmaceutical care in outpatient ICI treatment, particularly focusing on the period of providing pharmaceutical recommendations.

MATERIALS AND METHODS

**Evaluation of Pharmaceutical Care** We retrospectively assessed pharmaceutical interventions in all patients at the Hokkaido University Hospital Outpatient Infusion Center from April 2017 to March 2020. The primary endpoint of this study was the period of providing pharmaceutical recommendations to ICI-treated patients, and the secondary endpoints were number, adoption rate, efficacy, and details of pharmaceutical interventions. Symptom improvement in the patients was evaluated in accordance with the Common Terminology Criteria for Adverse Events (version 4.0) by physicians and/or pharmacists at every visit. The present study was approved by the Institutional Review Board of the Hokkaido University Hospital (Approval No: 020-0045) and was conducted in accordance with the Declaration of Helsinki.

**Pharmaceutical Approach to Patient Care** The procedure of the pharmaceutical approach to patient care in our outpatient infusion center is shown in Fig. 1. Deadline of the infusion order was defined as the morning prior to the treatment. Pharmacists checked the regimens and adequacy of the examination order in detail during the day and consulted physicians if there were any problems. On the day of the infusion, after the decision of treatment implementation by physicians, the pharmacists at the infusion center checked the prescriptions, vital signs, and laboratory data again. After confirmation, the pharmacists started mixing the infusion drugs. In addition, the Japanese Society of Pharmaceutical Health Care and Sciences (JSPHCS)–certified oncology pharmacists conducted face-to-face pharmaceutical care whenever possible, such as evaluation of adverse events and associated pharmaceutical recommendations, adherence checking, and medication teaching to the patients administered anticancer agents before or after the physician’s examination at every visit. We defined pharmaceutical interventions as follows: (1) prescription questions, which were conducted before pharmaceutical counseling and (2) pharmaceutical recommendations, which were performed related to the counseling.

**Extraction of Data** Data on pharmaceutical interventions were extracted from the pharmacy ordering system (TOSHO, Tokyo, Japan). Detailed information such as patient characteristics and symptom improvement by medication recommenda-

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**Fig. 1.** Procedure for the Pharmaceutical Approach to Patient Care at the Hokkaido University Hospital Outpatient Infusion Center
tions was obtained from the medical records of patients.

**Statistical Analysis**  The differences in the ratio of pharmaceutical recommendations before and 3 months after ICI treatment initiation were assessed using Fisher’s exact probability test using JMP Pro 14 (SAS Institute Japan, Tokyo, Japan). The period was set as 3 months because the median time for the onset of irAEs such as skin toxicity and gastrointestinal, endocrine, hepatic, and pulmonary symptoms was approximately 3 months. Differences were considered statistically significant when p-values were less than 0.05.

**RESULTS**

**Details of ICI-Treated Patients and Pharmaceutical Counseling Count**  A total of 366 patients (3597 administrations) who were administered ICIs in the period were enrolled (Fig. 2). Patient characteristics and total pharmaceutical counseling counts are shown in Table 1. The ICI-administration count increased with each passing year. Nivolumab was administered the most, followed by pembrolizumab, atezolizumab, durvalumab, ipilimumab, and avelumab. The number of face-to-face pharmaceutical counseling also increased, and they were conducted to 73% of the patients with ICI treatment for three years; especially, almost all patients in 2019 (data not shown).

**Period of Providing Pharmaceutical Recommendations to ICI-Treated Patients**  We evaluated the difference in the implementation rate of pharmaceutical recommendations regarding irAEs and other than irAEs before and 3 months after ICI treatment initiation (Fig. 3). They were significantly higher in the first 3 months after ICI treatment initiation compared to after the duration.

**Details of Pharmaceutical Interventions**  Pharmaceutical intervention details are shown in Table 2. A total of 429

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Table 1. Details of ICI-Treated Patients and Pharmaceutical Counseling Count

|                          | Number       |
|--------------------------|--------------|
| Total patients administered ICI (administrations) | 366 (3597)   |
| Sex (male/female)        | 254/112      |
| Median age (range)       | 69 (28–95)   |
| Types of cancer          |              |
| Lung                     | 163          |
| Head and neck            | 66           |
| Kidney                   | 48           |
| Melanoma                 | 47           |
| Urothelial               | 18           |
| Gastric                  | 17           |
| MSI-H solid tumor        | 4            |
| Lymphoma                 | 1            |
| Merkel cell              | 1            |
| Mesothelioma             | 1            |
| ICI administrations      |              |
| 2017                     | 725          |
| 2018                     | 1185         |
| 2019                     | 1687         |
| Total                    | 3597         |
| Patients administered ICIs (administrations) |            |
| Nivolumab                | 180 (2148)   |
| Pembrolizumab            | 95 (917)     |
| Atezolizumab             | 37 (173)     |
| Durvalumab               | 32 (306)     |
| Ipilimumab               | 21 (44)      |
| Avelumab                 | 1 (9)        |
| ICI administration in each treatment period |         |
| > 3 months               | 1239         |
| 3 ≤ months               | 2358         |
| Pharmaceutical counseling count | 2625 |

ICI, immune checkpoint inhibitors; MSI-H, microsatellite instability high.
interventions were performed. Approximately 70% of the prescription questions were suggestions regarding the ordering of laboratory examination. The questions conducted on the day of the administration were approximately 20%, resulting in four treatment suspensions. Pharmaceutical recommendations regarding irAEs were categorized into medication recommendations (81.1%), examination recommendations (10.8%), and recommendation of expert consultation (8.1%). The irAEs in the pharmaceutical recommendations were skin toxicity (68%), stomatitis (8%), and thyroid dysfunction and digestive symptoms (4%). The adoption rate of prescription questions was 86.5% in total and 37.7% for the day of administration. In contrast, most pharmaceutical recommendations were adopted. Figure 4 shows the rate of irAE symptom improvement by medication recommendations, suggesting 70% attenuation.

DISCUSSION

In this study, we evaluated pharmaceutical interventions, especially the effectiveness and implementation period of pharmaceutical recommendations in outpatient ICI treatment. Prescription questions were raised in approximately 8% of the patients administered ICI, and 70% of these were regarding suggestion on the ordering of laboratory examination. Although most physicians use laboratory test sets, they sometimes make errors in their use; therefore, their timing was broadly based (data not shown). The total adoption rate of questions was 86.5%, whereas the adoption rate on the day of the injection was 37.7%, which was similar to the results of our previous study.1 Although this rate is significantly lower than that of other questions or pharmaceutical recommendations, all questions on the injection day were regarding the patient’s condition, such as vital signs and laboratory data, resulting in four counts of treatment abeyance. Thus, multiple confirmation by several medical staff in addition to physicians is essential to provide safe cancer medication.

In terms of pharmaceutical recommendations, it was highly adopted, which was similar to that observed in previous studies.1,22 In addition, symptom improvement by medication recommendations was documented in 70% of the patients, similar to that in previous reports.1,2,23 Thus, it was demonstrated that pharmaceutical recommendations have a certain level of symptom amelioration efficacy, suggesting the necessity of affirmative face-to-face pharmaceutical care in outpatient ICI treatment.

As described above, successive pharmaceutical care could be the best method, however, it is important to understand the most crucial period for managing irAEs for more adequate and efficient pharmacy practice. It has been reported that frequent irAEs such as skin toxicity, hypothyroidism, interstitial lung disease, and diarrhea appear in the relatively early phase of treatment, and it is difficult to predict their frequency.20,21 We evaluated the period of providing pharmaceutical recommendations. Our results revealed that the recommendations

| Pharmaceutical Intervention Details | Number (%) |
|-------------------------------------|------------|
| Pharmaceutical interventions in ICI-treated patients | 429 |
| Prescription questions | 282 |
| Pharmaceutical recommendations | 147 |

| Details of prescription questions in ICI-treated patients | |
|----------------------------------------------------------|---|
| Laboratory examination ordering | 198 (70.2%) |
| Patient’s laboratory data and vitals on the day | 53 (18.8%) |
| Others | 31 (11.0%) |
| Suspensions of the treatment owing to the question | 4 |

| Types of pharmaceutical recommendations regarding irAEs | |
|--------------------------------------------------------|---|
| Medication recommendations | 60 (81.1%) |
| Examination recommendations | 8 (10.8%) |
| Recommendation of expert consultation | 6 (8.1%) |

| Details of recommendations in ICI-treated patients | |
|---------------------------------------------------|---|
| irAEs | 74 |
| Skin toxicity | 50 |
| Stomatitis | 6 |
| Thyroid dysfunction | 3 |
| Digestive symptoms | 3 |
| Diarrhea | 2 |
| Adrenal insufficiency | 2 |
| Blood pressure elevation | 2 |
| Others | 8 |
| Other than irAEs | 73 |
| Pain control | 30 |
| Adjustment of dosage and amount of medicines | 17 |
| Alteration to more favorable medicines | 8 |
| Constipation | 6 |
| Electrolyte revision | 3 |
| Dental problems | 2 |
| Neuropathy | 2 |
| Opioid-induced nausea | 2 |
| Others | 3 |

| Adoption rate of pharmaceutical interventions in ICI-treated patients | |
|---------------------------------------------------------------|---|
| Prescription questions | 86.5% |
| Conducted on the day of the administration | 37.7% |
| Pharmaceutical recommendations | 96.0% |

ICI: immune checkpoint inhibitors, irAEs: immune-related adverse events.

Fig. 4. Rate of Immune-Related Adverse Events Symptom Improvement by Medication Recommendations
regarding both irAEs and other than irAEs provided prior to 3 months from ICI treatment initiation were significantly more than those provided 3 months after. Moreover, most of the recommendations after this duration were repeatedly provided in patients with symptoms during the earlier period (data not shown). The results obtained in this study suggest that 3 months from ICI treatment initiation is the most important period for face-to-face pharmaceutical care, and this period is also recognized to be significant in patient education. We should consider the duration of care in light of these results, patient’s condition or problems, and irAE complications. If it is difficult to provide or continue pharmaceutical care, it is suitable to develop handling manuals to deal with irAEs according to guidelines, and adopt agreements such as collaborative drug therapy management or protocol-based pharmacotherapy management, which are reported to be meaningful in chemotherapy management, or organize a cooperative system with community pharmacies.

This study has some limitations in evaluating pharmaceutical care in ICI treatment. First, this study was retrospective and was conducted at a single institution without a control group. Second, as all pharmaceutical recommendations following pharmaceutical counseling were conducted by oncology specialized pharmacists, the results could differ from those of non-specialized pharmacists. In addition, our pharmaceutical approach and medical systems could be different from those in other countries. Third, we were not able to assess the influence on ICI efficacy. Electronic patient-reported outcomes for symptom monitoring have been shown to contribute to high-quality cancer care, resulting in good clinical outcomes. The investigators speculated that early responsiveness, such as symptom management counseling, supportive medications, chemotherapy dose modifications, and referrals for patient symptoms, is one potential mechanism of action that prevented adverse downstream consequences. Since irAE development is associated with clinical outcomes, specialist pharmaceutical approaches may affect ICI efficacy. Thus, further studies are needed to investigate the efficacy. Finally, evaluation from the perspective of patients is necessary.

In conclusion, we demonstrated the usability of pharmaceutical care in outpatient ICI treatment. Face-to-face pharmaceutical counseling up to 3 months from treatment initiation is the most important, as it contributes to useful care, resulting in improvement in the patient’s QOL and safe ICI treatment. The results obtained in this study will help construct a more improvement in the patient’s QOL and safe ICI treatment.

**Author Contributions** Participated in research design: YS, KU, and TS. Conducted experiments: YS. Performed data analysis: YS, KU, and TS. Wrote or contributed to the writing of the manuscript: YS, KU, TS, KY, KK, YT, YK, and MS.

**Conflict of Interest** YS, KU, TS, KY, KK, YT, and MS have no conflicts of interest. YK reports honoraria from Pfizer, Novartis and Bayer, and research funding from Eli Lilly, MSD, Ono Pharmaceutical, Novartis, Bayer, Chugai Pharma, Yakult, and Taiho and has provided speaker services to Eli Lilly, Chugai Pharma, Merck Serono, Novartis, Pfizer, Bayer, and Taiho.

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