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2022-05, ISPOR 2022, Washington, DC, USA

A real-world study to evaluate the effect of community pharmacy-based pharmaceutical care on the management of mild to moderate adverse events among cancer patients taking PD-1/PD-L1 in China

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Background

- Immune checkpoint inhibitors (ICIs) have been accepted as a standard-of-care therapeutic among various cancer types and dramatically improved patients' clinical outcomes.
- As a result of clinical autoimmunity, a large proportion of patients receiving ICIs treatment might experience immune-related adverse events (irAEs) [1-2].
- Although the development of irAE was found to be a predictor of better treatment response, study also showed that treatment interruption due to irAEs was a risk factor of poor prognosis [3].
- Active patient management services could promote the prognosis of cancer [4-5]. Therefore, as an important part of patient management and service, community pharmacy could play a key role in the management of cancer patients outside hospital.

Objectives

- Using data routinely collected from 79 Sipai community pharmacies in China, this study aims to understand the incidence of patient reported AE and evaluate the effect of a telephone based follow-up service provided by community pharmacists on the management of mild to moderate AEs among patients using PD-1/PD-L1.

Methods

- This is a real-world study using data routinely collected from 79 Sipai community direct-to-patient (DTP) pharmacies during their daily business activities between January 1, 2019 and March 31, 2021(Fig 1).
- De-identified records of medication purchase/refill and patient follow-up contacts were extracted from Sipai's data system according to predefined eligibility criteria.
- All patient reported AEs were screened and information about AE's type (according to CTCAE 5.0), severity (mild, moderate and severe), manner of management (pharmacy-based care, PBC vs. hospital-based management, HBM) and outcome (improved vs. not improved) were retrieved.
- If an AE was managed under the instruction of community pharmacist during regular telephone follow-up, the manner of management would be defined as PBC; if an AE was reported to be managed by a physician in hospital, the management manner would be defined as HBM.
- This study was approved by Shanghai Ethics Committee for Clinical Research (SECCR/2021-104-01).

Eligibility Criteria

- The first purchase of PD-1/PD-L1 drugs was made between January 1, 2019 and March 31, 2021.
- Cancer type was not missing in drug purchase data.
- Key information about AE (AE category/treatment method/grade/outcome, etc.) were not missing in follow-up data.

Statistical Analyses

- Descriptive statistics (number, percentage) were used to report AE incidence.
- Chi square test or Fisher exact test were used for comparison between groups.
- Univariate logistic regression was used to calculate odds ratio (OR) of AE improvement while comparing the two models of AE management.

Methods

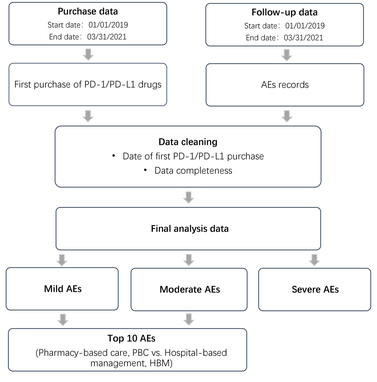

Figure 1. Study design and data flowchart

Results

Incidence and distribution of adverse events

- A total of 12102 adverse events were reported by 6661 patients, among which 65.53% were mild, followed by moderate (28.57%) and severe (5.89%) (Fig 2). Among the 7931 mild AEs, 4093 (51.61%) were managed by PBC, 3838 (48.39%) were managed by HBM. Over 80% of moderate AEs and almost all severe AEs (95.65%) were managed by HBM (Fig 3).
- Among all adverse events, 4794 were managed by PBC and 7308 were managed by HBM (Table 1). The distribution of AE severity was statistically significant different between the two groups ($p < 0.001$). The percentages of mild and moderate AEs were 85.38% and 13.98% in PBC group, and 52.52% and 38.15% in HBM group (Table 1).

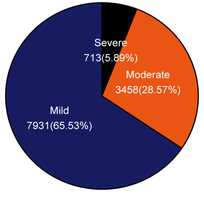

Figure 2. Severity distribution of all AEs

Results

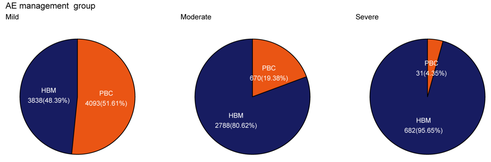

Figure 3. Distribution of mild, moderate and severe AEs

Table 1. Distribution of AEs severity in PBC and HBM groups

AEs severity, n (%)	PBC (n=4794)	HBM (n=7308)	P<0.001
Mild	4093 (85.38)	3838 (52.52)	
Moderate	670 (13.98)	2788 (38.15)	
Severe	31 (0.65)	682 (9.33)	

Table 2. Comparison of adverse event outcomes between PBC and HBM

Improvement rate, % (n/N)	Total	PBC	HBM	p
Mild	77.70(6162/7931)	77.33 (3165/4093)	78.09 (2997/3838)	0.432
Moderate	70.85 (2450/3458)	68.66 (460/670)	71.38 (1990/2788)	0.179
Severe	63.53 (453/713)	58.06 (18/31)	63.78 (435/682)	0.648

Improved outcomes of AEs

- The overall improvement rates for mild, moderate and severe AEs were 77.70%, 70.85% and 63.53%, respectively (Table 2).
- Among 7931 mild AEs, the improvement rates for PBC and HBM were 77.33% and 78.09% (P=0.432) (Table 2). Similar outcomes were also observed in eight out of ten most common mild AEs (Table 3). However, HBM showed superiority in the management of skin and subcutaneous tissue lesion (OR=1.39, P=0.014) and vascular disease (OR=5.22, P=0.004) (Fig 5).
- No statistically significant differences were observed between PBC and HBM in the effect of moderate AEs management neither as a whole (68.66% vs. 71.38%, p=0.179) (Table 2) nor by AE types (Table 4 and Fig 7).
- The majority of severe AEs was managed by the HBM and the improvement rate was 63.78% (Table 2).
- The top 10 mild AEs accounted for 95.65% of all mild AEs. The overall improvement was the highest in vascular diseases (89.66%) and the lowest in neurological disease (63.19%) (Fig 4).
- Among the top 10 moderate AEs (3205, 92.68%), vascular disease had the highest improvement rate (86.79%) and metabolic and nutritional malnutrition had the lowest improvement rate (51.67%) (Fig 6).

Limitations

The collection and recording of all AE related information in this study were based on patients' self-report and pharmacist's personal judgment, which may have the risk of information bias. Moreover, the selection of AE management method might subject to selection bias induced by patients' perceived severity of AE within the mild/moderate levels.

Table 3. Differences in improved outcomes of mild AEs between groups

Top 10 mild AEs improvement rate, % (n/N)	PBC	HBM	p
The general condition and medication performance	79.93 (916/1146)	77.16 (767/994)	0.132
Gastrointestinal diseases	80.19 (741/924)	83.60 (627/750)	0.084
Skin and subcutaneous tissue lesion diseases	78.61 (812/1033)	83.65 (491/587)	0.017
Metabolism and malnutrition	65.39 (291/445)	67.29 (181/269)	0.663
Respiratory, thoracic and mediastinal diseases	73.62 (120/163)	72.24 (229/317)	0.831
Medical examination	83.33 (75/90)	79.93 (231/289)	0.574
Neurological diseases	67.12 (49/73)	60.55 (66/109)	0.457
Skeletal muscle and connective tissue diseases	81.25 (39/48)	69.23 (72/104)	0.175
Vascular disease	76.32 (29/38)	94.39 (101/107)	0.004
Infection and infectious diseases	63.16 (24/38)	67.74 (42/62)	0.801

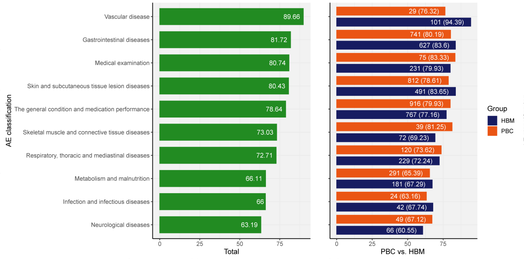

Figure 4. Ranking of improvement rates of the top ten mild AEs

Table 4. Differences in improved outcomes of moderate AEs between groups

Top 10 moderate AEs improvement rate, % (n/N)	PBC	HBM	p
The general condition and medication performance	66.16 (131/198)	63.97 (396/619)	0.635
Gastrointestinal diseases	72.41 (84/116)	75.00 (384/512)	0.646
Skin and subcutaneous tissue lesion diseases	79.87 (127/159)	76.79 (268/349)	0.509
Medical examination	62.96 (17/27)	77.51 (262/338)	0.139
Respiratory, thoracic and mediastinal diseases	58.33 (21/36)	71.15 (222/312)	0.163
Metabolism and malnutrition	49.25 (33/67)	53.10 (60/113)	0.73
Infection and infectious diseases	69.23 (9/13)	75.49 (77/102)	0.735
Vascular disease	90.91 (10/11)	86.32 (82/95)	1
Neurological diseases	38.46 (5/13)	58.33 (35/60)	0.318
Skeletal muscle and connective tissue diseases	54.55 (6/11)	74.07 (40/54)	0.275

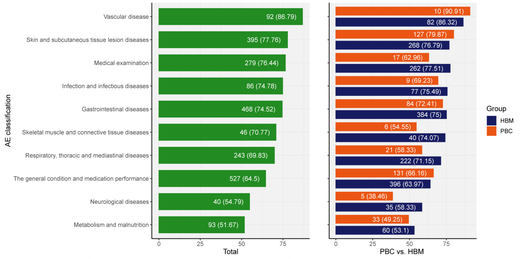

Figure 6. Ranking of improvement rates of the top ten moderate AEs

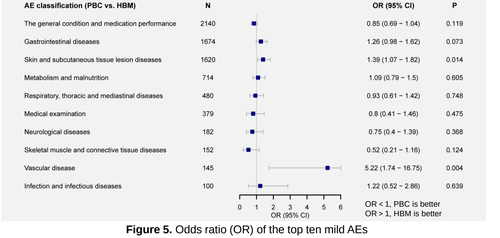

Figure 5. Odds ratio (OR) of the top ten mild AEs

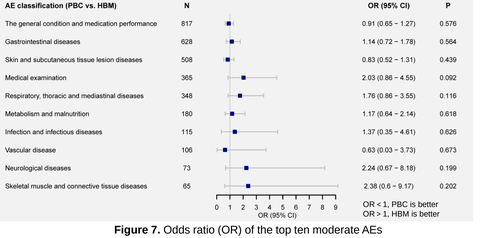

Figure 7. Odds ratio (OR) of the top ten moderate AEs

Conclusions

Nearly two-thirds of self-reported AE in patients taking PD-1/PD-L1 patients were mild, and more than half of them were managed by DTP pharmacies during their daily practice. For the majority of mild AEs, counseling and guidance services provided by community pharmacists through active telephone follow-up can achieve similar outcome as those managed by physicians in hospitals. Pharmacy-based care provided by community DTP pharmacies could play a positive role in the management of mild to moderate AEs among patients using PD-1/PD-L1.

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