



Inflammatory bowel disease associated with the combination treatment of nivolumab and metformin: data from the FDA adverse event reporting system

Huaqiang Zhou^{1,2,3,4} · Jiaqing Liu⁴ · Yaxiong Zhang^{1,2,3} · Li Zhang^{1,2,3}

Received: 15 November 2018 / Accepted: 27 December 2018 / Published online: 8 January 2019
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Abstract

Purpose PD-1/PD-L1 inhibitors have demonstrated unparalleled therapeutic efficacy in multiple tumor types. Additionally, metformin has been linked to favorable outcomes in tumors. Many researchers have reported immune-mediated adverse events induced by immune checkpoint inhibitors (ICI) single agent. However, little is documented on the adverse events of the combined use of ICI and metformin.

Methods To address this question, we used the Food and Drug Administration Adverse Event Reporting System (FAERS) to display the landscape of adverse events associated with the combined use of ICI and metformin. We identified 38 adverse event cases about the combination treatment between January 1, 2015 and June 30, 2018.

Results There are 36 cases in patients receiving nivolumab plus metformin (NM) therapy, and the other 2 cases were pembrolizumab plus metformin (PM). Among the 36 patients receiving NM therapy, the most common indication was for treatment of malignant lung cancer (20, 55.56%), Notably, 9 cases of inflammatory bowel disease (IBD) and diarrhea were reported.

Conclusions Our findings revealed that higher risk of IBD might occur in lung cancer patients during the combined therapy of nivolumab plus metformin. Further studies are needed to verify our findings.

Keywords Immune checkpoint inhibitors · Metformin · Adverse event · FAERS · Inflammatory bowel disease

Huaqiang Zhou, Jiaqing Liu and Yaxiong Zhang contributed equally to this work.

✉ Li Zhang
zhangli6@mail.sysu.edu.cn

Huaqiang Zhou
liujiaosuan@gmail.com

Jiaqing Liu
drmayoliu@gmail.com

Yaxiong Zhang
zhangyx@sysucc.org.cn

¹ Department of Medical Oncology, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, Guangdong, People's Republic of China

² State Key Laboratory of Oncology in South China, Guangzhou, People's Republic of China

³ Collaborative Innovation Center for Cancer Medicine, Guangzhou, People's Republic of China

⁴ Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, People's Republic of China

Introduction

Immune checkpoint inhibitors (ICI) targeting the PD-1/PD-L1 axis have demonstrated unparalleled therapeutic efficacy in multiple tumor types, which are rapidly transforming the oncology practice [1]. Meanwhile, metformin has been linked to favorable outcomes in tumors through observational and experimental studies [2]. Researchers are conducting sundry randomisation clinical trials (RCTs) (single agents; combination with chemotherapy, tyrosine kinase inhibitor (TKI) and ICI therapy) to confirm the efficacy and safety of metformin. Immune-mediated adverse events induced by ICI single agent have been reported [3]. However, little is documented on the adverse events of the combined use of ICI and metformin. Therefore, we used the Food and Drug Administration Adverse Event Reporting System (FAERS) [4], to display the landscape of adverse events associated with the combined use of ICI and metformin.

Materials and methods

We used FAERS to analyse all reported adverse events between January 1, 2015 and June 30, 2018 that were associated with the combination treatment of FDA approved PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab) and metformin. Institutional review board approval was waived for this study because FAERS is a public anonymized database. All statistical analyses were performed using R software (version 3.4.2, Institute for Statistics and Mathematics, Vienna, Austria; <http://www.r-project.org>).

Results

We identified 38 adverse event cases about the combination treatment (PD-1/PD-L1 inhibitors + metformin), of which 10 (26.32%) resulted in death (Table 1). The number of cases increased over time, from 4 in 2015, to 22 in 2017, and now 8 in the first half of 2018. Most patients were men (34, 89.47%). The mean age was 65.76 years. The cases were collected from around the world, with France (9, 23.68%), Italy (9, 23.68%), and the United States (9, 23.68%) reporting most of the cases. The main report source was “Healthcare Professional” (35, 92.11%).

There are 36 cases in patients receiving nivolumab plus metformin (NM) therapy, and the other 2 cases were pembrolizumab plus metformin (PM). Among the 36 patients receiving NM therapy, the most common indication was for treatment of malignant lung cancer (20, 55.56%), in which 13 patients were diagnosed with diabetes mellitus. Notably, 9 cases of inflammatory bowel disease (IBD) and diarrhea were reported. For hepatocellular carcinoma ($N=6$), multiple organ dysfunction syndrome and lactic acidosis were the most common adverse event. Three patients with metastatic malignant melanoma (with diabetes mellitus) were exposed to interstitial lung disease. Two patients with malignant melanoma received PM therapy, and they reported the cases of decreased thyroglobulin, acute kidney injury, and pancreatic failure.

To further explore the relationship between IBD and the combination treatment, we analysed 36,815 PD-1/PD-L1 inhibitors cases without metformin during the period reviewed. A total of 60 IBD cases were reported, with a crude reporting ratio of 0.16%. In addition, we observed that 20 cases of IBD in 23,572 patients receiving metformin were reported to the FAERS, including 9 cases in NM therapy we mentioned. The remained 11 IBD adverse events existed among patients (receiving metformin, without PD-1/PD-L1 inhibitors) diagnosed with diabetes

Table 1 Characteristics of patients receiving immune checkpoint inhibitor and metformin (Data from the FDA Adverse Event Reporting System, 2015–2018, $N=38$)

Characteristic	<i>N</i> (%)
Male gender	34 (89.47)
Age (Mean)	65.76
Cancer	
Lung	20 (52.63)
Liver	6 (15.79)
Melanoma	5 (13.16)
Others	7 (18.42)
Region	
France	9 (23.68)
Italy	9 (23.68)
United States	9 (23.68)
Canada	3 (7.89)
Japan	3 (7.89)
Others	5 (13.16)
Reporting year	
2015	4
2016	4
2017	22
2018 (30/6)	8
Regimen	
Nivolumab + Metformin	36 (94.74)
Pembrolizumab + Metformin	2 (5.26)
Adverse events ($N>2$)	
Diarrhea	10
Inflammatory bowel disease	9
Lactic acidosis	7
Multiple organ dysfunction syndrome	6
Renal failure	6
Pneumonitis	4
Interstitial lung disease	3
Dyspnea/tachypnoea	3/2
Acute kidney injury	2
Diabetic ketoacidosis	2
Drug eruption	2

mellitus, rather than malignancies. Notably, no IBD was reported in cases receiving metformin combined with TKI or chemotherapy.

Discussion

Immunotherapy has become a standard of care options for several malignancies. Considering that there is a substantial proportion of cancer patients concomitant with diabetes mellitus, the combined usage of ICI and metformin may be inevitable in the clinical practice. At present, little is

documented about the adverse events of the combined use of ICI and metformin. The relevant RCTs are ongoing, and the data is not yet available. Besides, it is time-consuming to collect safety data from clinical trials, with costs in manpower and material resources involved. Thus, we subtly summarized the currently reported adverse events and detected potential high-risk adverse events through FAERS, ahead of the publication of formal RCTs. Our findings suggested that higher risk of IBD might occur in lung cancer patients concomitant with diabetes mellitus during the combined therapy of nivolumab plus metformin, which has not hitherto been reported in literatures. Although our data were obtained from FAERS, a simple database with a paucity of details, the number of IBD cases reported is still alarming. Since IBD significantly influences health-related quality of life [5], further studies are needed to identify mechanisms and predictors of IBD associated with the combined therapy of immune checkpoint inhibitors and metformin.

This study has several limitations. The detailed information for patients is not available in the FAERS. In addition, FAERS post-marketing data are subject to many biases, and they cannot ascertain causality or incidence. Despite these limitations, these data can offer an update for oncologists. We suggest oncologists to closely follow-up patients with IBD from these agents, while awaiting the formal release of all trial data.

Acknowledgements Wenfeng Fang, Shaodong Hong, Gang Chen, Shen Zhao, Xi Chen, Zhonghan Zhang (all with the Sun Yat-sen University Cancer Center), provided data interpretation and critical revision of the manuscript. Yunpeng Yang, Yuanyuan Zhao, Yan Huang, and Hongyun Zhao (all with the Sun Yat-sen University Cancer Center), contributed excellent work to the conception and design of the study. None of these individuals received financial compensation.

Author contributions LZ supervised this work. HZ, JL, YZ were responsible for the conception and design of the study, interpretation

of data, drafting, and writing of the article. All authors participated in final approval of the article and agreed to be accountable for all aspects of the work.

Funding This work was supported by: National Key R&D Program of China (Grant No. 2016YFC0905500, 2016YFC0905503). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Compliance with ethical standards

Ethics approval and consent to participate Institutional review board approval was waived for this study because FAERS is a public anonymized database.

Conflict of interest The authors declare that they have no conflict of interest.

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