



· 论 著 ·

PD-1单抗治疗非小细胞肺癌相关不良反应及其与疗效的相关性分析

义维丽¹, 赵文成², 黄东宁¹, 覃莉¹, 吴新天¹, 周斐², 吴凤英²

1. 柳州市工人医院肿瘤科, 广西柳州 545005;
2. 同济大学附属上海市肺科医院肿瘤科, 上海 200433

[摘要] 背景与目的: 随着免疫检查点抑制剂在肺癌中的应用增多, 免疫相关不良反应 (immune-related adverse event, irAE) 受到越来越多的重视。分析使用单药免疫治疗肺癌患者的irAE发生情况及其与免疫治疗效果的相关性。方法: 回顾性收集同济大学附属上海市肺科医院2015年6月—2019年1月接受抗程序性死亡 [蛋白] -1 (programmed death-1, PD-1) 免疫治疗的晚期非小细胞肺癌患者的基线临床资料、irAE发生的种类、时间、严重程度、处理、转归以及免疫治疗效果 [客观缓解率 (objective response rate, ORR)、疾病控制率 (disease control rate, DCR)、无进展生存期 (progression-free survival, PFS)] 等资料。使用SPSS 23.0软件, 探讨irAE与患者免疫治疗效果的相关性。结果: 共109例患者入组, 中位年龄64岁 (32~82岁), 男女比例为89:20, ECOG体能状态评分0、1、2分者分别为4、103、2例, 接受一线、二线、三线及以上治疗的患者分别为15、65、29例。63例 (57.8%) 患者发生irAE, 其中43例出现复合irAE, 常见irAE为皮肤反应 (28例, 25.7%)、免疫性肝炎 (18例, 16.6%)、疲乏 (16例, 14.7%)、内分泌系统毒性 (15例, 13.8%)、免疫性肺炎 (12例, 11.0%) 及胃肠道反应 (10例, 9.2%) 等; irAE常见于6~27周, 10例 (9.2%) 患者发生了3~4级irAE, 主要为免疫相关性肺炎。总人群ORR为24.7%, DCR为77.9%, 中位PFS为4.6个月 (95% CI: 3.9~5.2)。irAE组对比非irAE组有着较高的ORR (36.5% vs 8.7%, $P=0.001$) 和中位PFS (8.7个月 vs 3.5个月, $HR=0.294$, 95% CI: 0.184~0.469, $P<0.001$), 其中皮肤不良反应与预后最为相关: 中位PFS为12.7和4.3个月 ($HR=2.332$, 95% CI: 1.184~4.595, $P=0.014$)。结论: 肺癌irAE多见于治疗后6~27周, 多为1~2级, 其中3~4级irAE多为免疫性肺炎, irAE发生与疗效相关。

[关键词] 非小细胞肺癌; 程序性死亡 [蛋白] -1; 免疫相关不良反应; 疗效

DOI: 10.19401/j.cnki.1007-3639.2021.03.007

中图分类号: R734.2 文献标志码: A 文章编号: 1007-3639(2021)03-0203-09

Analysis of immune-related adverse events and its correlation with efficacy of anti-PD-1 monotherapy in advanced non-small cell lung cancer YI Weili¹, ZHAO Wencheng², HUANG Dongning¹, QIN Li¹, WU Xintian¹, ZHOU Fei², WU Fengying² (1. Department of Oncology, Liuzhou Workers' Hospital, Liuzhou 545005, Guangxi Zhuang Autonomous Region, China; 2. Department of Oncology, Shanghai Pulmonary Hospital, Tongji University, Shanghai 200433, China)

Correspondence to: WU Fengying E-mail: fywu@163.com

[Abstract] **Background and purpose:** With the increasing application of immune checkpoint inhibitors in lung cancer, immune-related adverse event (irAE) has attracted more and more attention. This study aimed to analyze the occurrence of irAE in patients receiving single-drug immunotherapy and the correlation between irAE and immunotherapy efficacy. **Methods:** Data of patients with advanced non-small cell lung cancer (NSCLC) treated with anti-programmed death-1 (PD-1) monotherapy in Shanghai Pulmonary Hospital, Tongji University from June 2015 to January 2019 were collected. Patients' baseline clinical data, irAE types, occurrence time, severity, management of irAE, the objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS) were retrospectively analyzed. And then, we used the SPSS 23.0 software to explore the correlation between irAE and PFS. **Results:** One hundred and nine advanced NSCLC patients were treated in our hospital. The median age of the patients was 64 years (range

基金项目: 国家自然科学基金青年基金 (81402381); 促进市级医院临床技能与临床创新能力三年行动计划 (SHDC2020CR4001)。
通信作者: 吴凤英 E-mail: fywu@163.com

32-82 years). The ratio of male to female was 89 : 20. The ECOG performance status scores of 0, 1 and 2 were 4, 103 and 2 cases respectively. The number of patients who received the first-line, second-line and third-line and above treatment were 15, 65 and 29 respectively. At the data cutoff, irAE occurred in 63 patients (57.8%). Among them, 43 cases had complex irAE. The most common irAE were skin adverse events ($n=28$, 25.7%). Other irAE were liver dysfunction ($n=18$, 16.6%), fatigue ($n=16$, 14.7%), endocrine toxicity ($n=15$, 13.8%), immune-related pneumonitis ($n=12$, 11.0%) and gastrointestinal toxicity ($n=10$, 9.2%). Most irAE occurred between 6 and 27 weeks. Ten patients (9.2%) had grade 3-4 irAE, mainly immune-related pneumonitis. Among the overall population, ORR was 24.7%, DCR was 77.9%, and median PFS was 4.6 months (95% CI: 3.9-5.2). Patients with irAE had significantly higher ORR compared with patients who did not have irAE (36.5% vs 8.7%, $P=0.001$). Similarly, the median PFS among patients with irAE was longer than patients without irAE (8.7 months vs 3.5 months, HR=0.294, 95% CI: 0.184-0.469, $P<0.001$). Among them, skin adverse events were most correlated with prognosis (median PFS: 12.7 months vs 4.3 months, HR=2.332, 95% CI: 1.184-4.595, $P=0.014$). **Conclusion:** Most cases of irAE in immunotherapy of lung cancer occurred in 6-27 weeks of treatment, and most of them were grade 1-2. Grade 3-4 irAE were mostly immune-related pneumonitis. Development of irAE was associated with survival outcome.

[Key words] Non-small cell lung cancer; Programmed death-1; Immune-related adverse events; Efficacy

肺癌是发病率和死亡率最高的恶性肿瘤, 2018年全球癌症统计数据显示, 肺癌占全球恶性肿瘤总发病人数的11.6%, 因肺癌死亡人数占癌症相关总死亡人数的18.4%^[1]。在中国, 肺癌发病率和死亡率均居第1位, 严重威胁着人类健康^[2]。约80%的肺癌为非小细胞肺癌 (non-small cell lung cancer, NSCLC), 多数患者初诊时已是晚期, 近年来针对免疫检查点程序性死亡 [蛋白] -1 (programmed death-1, PD-1) / 程序性死亡 [蛋白] 配体-1 (programmed death ligand-1, PD-L1) 抑制剂的免疫治疗给晚期肺癌的治疗带来了曙光。PD-1抑制剂如纳武利尤单抗 (nivolumab)、帕博利珠单抗 (pembrolizumab) 已被证实能显著延长晚期 NSCLC 患者的生存期, 均获批用于晚期 NSCLC 的标准二线治疗^[3-5], pembrolizumab 获批用于一线联合治疗或单药用于 PD-L1 表达 >50% 的 NSCLC 患者^[6]。免疫治疗相对安全, 但也可能发生免疫相关不良反应 (immune-related adverse event, irAE), 随着免疫治疗在临床中应用的增多, irAE 也日益被重视。目前肺癌免疫治疗的 irAE 报道多见于大型的 III 期临床研究, 而这些大型的全球性临床研究多为高加索人种, 而其中亚裔人群, 尤其是中国人群的数据相对较少。另外, 国内很多自主研发的免疫抑制剂安全性数据不详。因此, 本研究汇总分析了同济大学附属上海市肺科医院使用单药 PD-1 抑制剂的 irAE 发生情

况及其与免疫治疗效果的相关性。

1 资料和方法

1.1 研究对象

回顾性分析同济大学附属上海市肺科医院 2015年6月—2019年1月接受抗 PD-1 抑制剂单药治疗的局部晚期及晚期 NSCLC 患者 (包括入组临床研究及非临床研究的患者)。收集患者的临床基本特征、PD-1 治疗的种类和方法, 收集 irAE 的种类、发生时间、严重程度、处理和预后。irAE 如皮肤反应、胃肠道反应、免疫性肝炎、内分泌系统毒性等分级、分类标准采用美国国家癌症研究所通用不良事件术语标准 4.0 版 (Common Terminology Criteria for Adverse Events version 4.0, CTCAE v4.0) 评估。

1.2 方法

收集疗效数据, 疗效评估使用实体瘤疗效评价标准 (Response Evaluation Criteria in Solid Tumors, RECIST) 1.1 版本, 对评估为疾病进展 (progressive disease, PD) 的患者在 4~8 周后经 RECIST 评估再确认, 收集客观缓解率 (objective response rate, ORR)、疾病控制率 (disease control rate, DCR)、无进展生存期 (progression-free survival, PFS)。随访截至 2019年6月1日。按有无 irAE 发生分为两组: irAE 组及非 irAE 组。

1.3 统计学处理

使用SPSS 23.0软件,分析两组患者基线临床特征,年龄采用描述性统计分析及独立样本 t 检验。两分类变量如吸烟状态、性别。有效率ORR、DCR等采用Pearson χ^2 检验。免疫治疗线数、病理学类型、放射治疗史等采用 $R \times C$ 表 χ^2 检验分析。总人群及两组患者PFS采用Kaplan-Meier法和log-rank进行检验分析。单因素Kaplan-Meier法及多因素COX回归风险比例模型方法分析探讨irAE与患者PFS的相关关系, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 人群基线特征

2015年6月—2019年1月,共109例患者接受了PD-1抑制剂单药免疫治疗,基线特征如下:中位年龄64岁(32~82岁),男女比例为89:20, ECOG体能状态(performance status, PS)评分0、1、2分者分别为4、103、2例,吸烟或既往吸烟、从不吸烟者分别为69、40例,Ⅲ、Ⅳ期分别为20、89例,腺癌、鳞癌、NSCLC-非特指型(NSCLC-not otherwise specified, NSCLC-NOS)、其他病理学类型分别为50、52、4、3例,免疫单药一线、二线、三线及以上患者分别为15、65、29例,接受免疫治疗药物种类分别为nivolumab、pembrolizumab、BGB-A317 [百济神州(北京)生物科技有限公司PD-1单抗]、SHR1210(江苏恒瑞医药股份有限公司PD-1单抗)、IBI308 [信达生物制药(苏州)有限公司PD-1单抗],患者数分别为25、60、17、3、4例。基因状态:野生型、未检测、EGFR突变、KRAS突变、BRAF突变为98、4、2、4、1例。PD-L1表达情况:阳性、阴性、未检测分别为11、8、90例,多数患者未检测PD-L1状态(90/109, 82.5%),19例检测的患者中PD-L1阳性($\geq 1\%$)有11例(10例为Ⅳ期,1例为Ⅲ期,表1)。

2.2 抗PD-1免疫治疗irAE

irAE发生情况:109例患者中,63例(57.8%)患者发生了irAE,其中43例(68.2%)

发生了复合irAE,20例(31.8%)为单一irAE。最常见irAE为皮肤反应(29例,25.7%),其次分别为免疫性肝炎(18例,16.6%)、疲乏(16例,14.7%)、内分泌系统毒性(15例,13.8%)、免疫性肺炎(12例,11.0%)及胃肠道反应(10例,9.2%)等;皮肤血管瘤仅见于使用SHR1210患者。irAE的发生情况和严重程度见表2和图1。

发生时间:irAE多于治疗后4~30周出现,最常见于6~27周。不同irAE起始时间不一样:皮疹反应为18.9周(0.2~38.5周),瘙痒为28.5周(8.0~50.0周),免疫性肝炎为27.1周(4.0~67.1周),免疫性肺炎为28.2周(6.3~69.3周),内分泌系统毒性为26.6周(4.0~40.0周),消化系统毒性为6.1周(2.7~14.2周),疲乏为24.0周(0.2~45.0周)等(图2)。

治疗和预后:共17例患者使用了激素冲击治疗,主要用于肺炎、结肠炎、肾炎、关节炎等,其中4例免疫性肺炎和1例免疫性结肠炎患者缓解后永久停止使用抗PD-1治疗,免疫性肺炎患者中1例患者肺炎治疗降级后更换化疗方案,3例患者因肿瘤进展更换治疗方案,1例患者因肿瘤进展未继续抗肿瘤治疗。3例肺炎患者及肾炎、关节炎等患者治疗降级后继续使用抗PD-1治疗。

2.3 irAE的特殊情况

复合irAE:43例患者发生复合irAE,其中最为常见的是皮疹合并免疫性肝炎(16/43, 37.2%),其次为皮疹合并乏力(10/43, 23.3%),免疫性肝损伤合并甲状腺功能异常(6/43, 13.9%),皮疹合并免疫性肺炎(5/43, 11.6%),免疫性肝炎合并腹泻(5/43, 11.6%)等。

严重irAE后再挑战患者包括:1例皮疹合并3级免疫性肺炎患者治疗降级后继续抗PD-1治疗,出现I度皮疹,未再次出现免疫性肺炎;1例患者因无症状性淀粉酶、脂肪酶Ⅲ级升高,停药后缓解,后继续抗PD-1治疗,再次出现1/2级irAE,未出现严重irAE。另外,有3例免疫性肺炎(2例2级,1例1级)、2例肾炎(1例1级,1例2级)及2例关节炎(均为2级)患者后续继续使用抗PD-1治疗未见irAE加重,用药至PD。

表 1 总人群基线特征

Tab. 1 Clinical characteristics of the total population

Clinical characteristic	[n (%)]			P value
	All patients (109)	irAE group (63)	Non-irAE group (46)	
Median age (range)/year	64 (32-82)	63 (32-82)	65 (39-82)	0.294
Gender				0.435
Male	89 (81.6)	53 (84.1)	36 (78.2)	
Female	20 (18.4)	10 (15.9)	10 (21.8)	
ECOG performance status				0.232
0	4 (3.6)	2 (3.1)	2 (4.3)	
1	103 (94.6)	61 (96.9)	42 (91.4)	
2	2 (1.8)	0 (0.0)	2 (4.3)	
Histological type				0.978
Adenocarcinoma	50 (45.9)	29 (46.0)	21 (45.6)	
Squamous	52 (47.7)	30 (47.6)	22 (47.8)	
NSCLC-NOS	4 (3.6)	2 (1.8)	2 (4.3)	
Other*	3 (2.7)	2 (1.8)	1 (2.2)	
Smoking status				0.097
Current or former smoker	69 (63.3)	44 (69.8)	25 (54.3)	
Never	40 (36.7)	19 (30.2)	21 (45.7)	
Clinical stage				0.825
III	20 (18.3)	12 (19.0)	8 (17.4)	
IV	89 (81.7)	51 (81.0)	38 (82.6)	
Gene mutation status				0.585
Wild type	98 (89.0)	56 (89.0)	42 (91.3)	
Undetected	4 (3.6)	3 (4.7)	1 (2.1)	
EGFR mutation	2 (1.8)	1 (1.6)	1 (2.1)	
KRAS mutation	4 (3.6)	3 (4.7)	1 (2.1)	
BRAF mutation	1 (0.9)	0 (0.0)	1 (2.1)	
PD-L1 expression (22C3)				0.535
Positive (TPS \geq 1%)	11 (10.0)	8 (12.7)	3 (6.5)	
Negative	8 (7.5)	4 (6.3)	4 (8.8)	
Undetected	90 (82.5)	51 (81.0)	39 (84.7)	
Immunotherapy				0.051
Nivolumab	25 (23.0)	12 (19.0)	13 (28.2)	
Pembrolizumab	60 (55.0)	31 (49.2)	29 (63.0)	
BGB-A317	17 (15.6)	13 (20.6)	4 (8.8)	
SHR1210	3 (2.7)	3 (4.7)	0 (0.0)	
IBI308	4 (3.6)	4 (6.3)	0 (0.0)	
Treatment lines				0.020
First line	15 (13.8)	10 (15.9)	5 (10.8)	
Second line	65 (59.6)	43 (68.2)	22 (47.8)	
Third line or higher	29 (26.6)	10 (15.9)	19 (41.4)	

*: Adenosquamous carcinoma in 2 cases, adenoid cystic carcinoma in 1 case; TPS: Tumor proportion score

表2 IrAE分类、分级

Tab. 2 The category and grade of irAE

Item	Total patients of any grade	Grade I - II	Grade III -IV	[n (%)]	
				Weeks to onset median (range)	Steroid therapy (yes/no)
Any irAE	63 (57.8)	54 (49.5)	9 (8.2)		
Skin irAE	28 (25.7)				No
Rash	20 (18.3)	19 (17.4)	1 (0.9)	18.9 (0.2-38.5)	
Pruritus	7 (6.4)	6 (5.5)	0 (0.0)	28.5 (8.0-50.0)	
Alopecia	1 (0.9)	1 (0.9)	0 (0.0)		
Cutaneous hemangioma	3 (2.7)	3 (2.7)	0 (0.0)		
Hepatotoxicity	18 (16.6)			27.1 (4.0-67.1)	No
Transaminase increased	16 (14.7)	16 (14.7)	0 (0.0)		
Blood bilirubin increased	2 (1.8)	2 (1.8)	0 (0.0)		
Lactic dehydrogenase increased	1 (0.9)	1 (0.9)	0 (0.0)		
Nephrotoxicity	2 (1.8)	2 (1.8)	0 (0.0)	NA	Yes
Neurotoxicity	2 (1.8)	2 (1.8)	0 (0.0)	NA	NA
Pneumonitis	12 (11.0)	7 (6.4)	5 (4.5)	28.2 (6.3-69.3)	Yes
Cardiotoxicity	1 (0.9)	1 (0.9)	0 (0.0)	NA	No
Endocrine toxicity	15 (13.8)			26.6 (4.0-40.0)	Yes
Hypothyroidism	3 (2.7)	2 (1.8)	1 (0.9)		
Hyperthyroidism	8 (7.3)	8 (7.3)	0 (0.0)		
Thyroiditis	1 (0.9)	1 (0.9)	0 (0.0)		
Diabetes	2 (1.8)	2 (1.8)	0 (0.0)		
Dyslipidemia	2 (1.8)	2 (1.8)	0 (0.0)		
Gastrointestinal toxicity	10 (9.2)			6.1 (2.7-14.2)	
Diarrhea	6 (5.5)	6 (5.5)	0 (0.0)		No
Constipation	4 (3.6)	4 (3.6)	0 (0.0)		No
Colitis	2 (1.8)	1 (0.9)	0 (0.0)		Yes
Nausea/vomiting	2 (1.8)	2 (1.8)	1 (0.9)		No
Pancreatitis	3 (2.7)			NA	No
Amylase/lipase increased	3 (2.7)	2 (1.8)	1 (0.9)		
Hematotoxicity	7 (6.4)			25.0 (3.0-35.7)	No
Anemia	4 (3.6)	4 (3.6)	0 (0.0)		No
Leukopenia/neutrophil count decreased	1 (0.9)	1 (0.9)	0 (0.0)		No
Thrombocytopenia	2 (1.8)	2 (1.8)	0 (0.0)		No
Musculoskeletal toxicity	4 (3.6)			NA	
Myositis/myalgia	2 (1.8)	2 (1.8)	0 (0.0)		No
Arthritis	2 (1.8)	2 (1.8)	0 (0.0)		Yes
Eye toxicity	3 (2.7)			NA	No
Blepharospasm	2 (1.8)	2 (1.8)	0 (0.0)		
Eye discomfort	1 (0.9)	1 (0.9)	0 (0.0)		
Dry mouth	6 (5.5)	6 (5.5)	0 (0.0)	38.5 (4.0-71.4)	No
Oral mucositis	3 (2.7)	3 (2.7)	0 (0.0)	NA	No
Infusion reaction	4 (3.6)	4 (3.6)	0 (0.0)	NA	No
Fatigue	16 (14.7)	16 (14.7)	0 (0.0)	24.0 (0.2-45.0)	No
Appetite loss	9 (8.2)	9 (8.2)	0 (0.0)	34.3 (0.6-42.8)	No
Weight loss	4 (3.6)	4 (3.6)	0 (0.0)	NA	No
Gum pain	7 (6.4)	7 (6.4)	0 (0.0)	25.7 (0.3-54.0)	No
Peripheral edema	3 (2.7)	3 (2.7)	0 (0.0)	NA	No

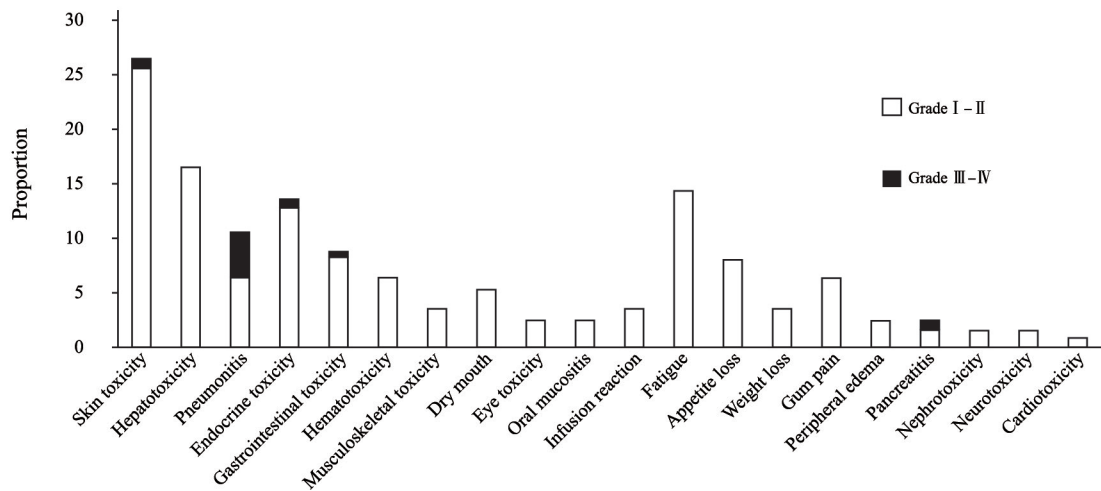


图 1 IrAE分类、分级

Fig. 1 The category and grade of irAE

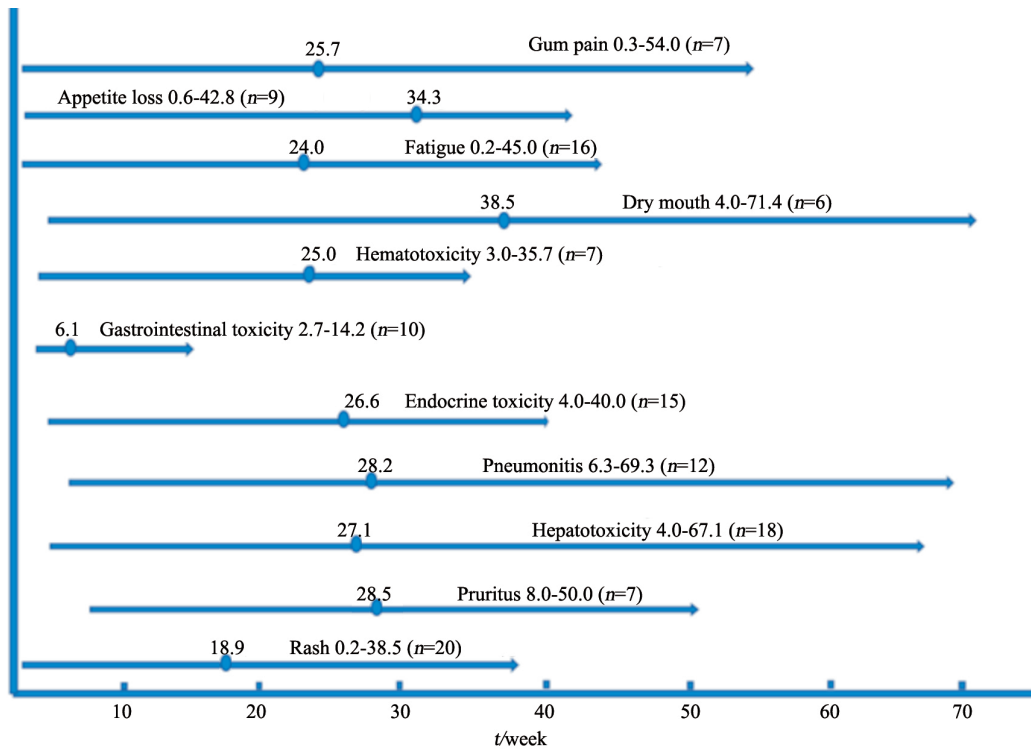


图 2 不同irAE发生的中位时间

Fig. 2 Median time to onset irAE for different toxicities

2.4 irAE与抗PD-1治疗效果的相关性

截至随访日期, 总人群ORR为24.7%, DCR为77.9%, irAE组对比非irAE组有较高的ORR及DCR (ORR: 36.5% vs 8.7%, $P=0.001$; DCR: 85.7% vs 67.4%, $P=0.023$, 表3)。总人群中位PFS为4.6个月 (95% CI: 3.9~5.2个月)。irAE组和非irAE组中位PFS分别为8.7和3.5个月 (HR=0.294,

95% CI: 0.184~0.469, $P<0.001$, 图3~4)。单因素分析显示, 免疫性肝炎 ($P=0.002$)、皮肤反应 ($P<0.001$)、口腔黏膜炎 ($P=0.003$)及牙龈疼痛 ($P=0.02$)与PFS预后相关; 多因素分析提示, 皮肤反应 ($P=0.014$)与疗效呈正相关, 中位PFS为12.7和4.3个月 (HR=2.332, 95% CI: 1.184~4.595, $P=0.014$, 表4, 图5)。

表 3 免疫治疗效果

Tab. 3 Response to immunotherapy

Response	All patients (109)	irAE group (63)	Non-irAE group (46)	<i>P</i> value
Partial response	27 (24.7)	23 (36.5)	4 (8.7)	
Stable disease	58 (53.2)	31 (49.2)	27 (58.7)	
Progressive disease	24 (22.1)	9 (14.3)	15 (32.6)	
Objective response rate	24.7%	36.5%	8.7%	0.001
Disease control rate	77.9%	85.7%	67.4%	0.023

表 4 免疫不良事件与PFS的关系

Tab. 4 Relationship between immune-related adverse events and PFS

PFS	Univariable HR (95% CI)	<i>P</i> value	Multivariable HR (95% CI)	<i>P</i> value
Skin toxicity	0.329 (0.187-0.576)	<0.001	2.332 (1.184-4.595)	0.014
Hepatotoxicity	0.367 (0.193-0.698)	0.002	1.926 (0.904-4.102)	0.089
Endocrine toxicity	1.619 (0.836-3.137)	0.153	1.078 (0.516-2.254)	0.842
Fatigue	1.616 (0.890-2.935)	0.115	0.952 (0.494-1.835)	0.884
Oral mucosal toxicity	3.877 (1.601-9.390)	0.003	2.352 (0.837-6.608)	0.105
Gum pain	0.299 (0.108-0.827)	0.020	2.098 (0.629-6.999)	0.228
Appetite loss	1.503 (0.711-3.178)	0.286	-	-
Gastrointestinal toxicity	0.949 (0.473-1.901)	0.882	-	-
Hematotoxicity	0.836 (0.336-2.081)	0.700	-	-
Pneumonitis	1.018 (0.539-1.922)	0.956	-	-

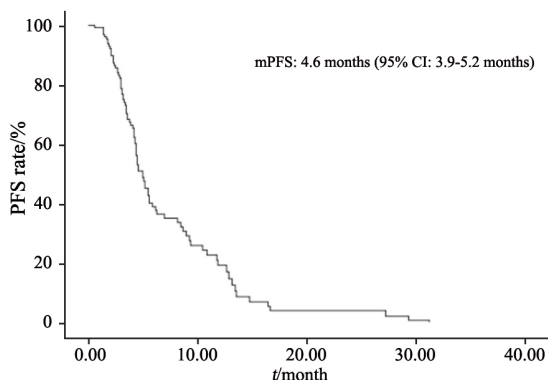


图 3 总人群的PFS

Fig. 3 PFS in total population

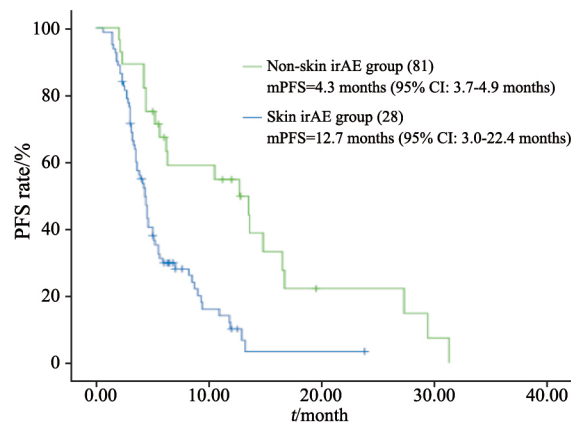


图 5 有无皮肤irAE患者的PFS

Fig. 5 PFS for patients with and without skin irAE

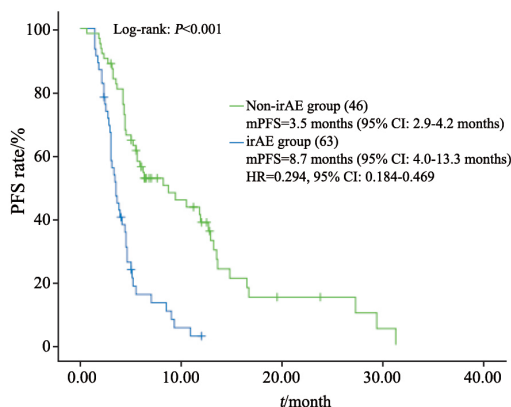


图 4 irAE组及非irAE组患者的PFS

Fig. 4 PFS for patients with and without irAE

3 讨论

PD-1/PD-L1抑制剂可阻断T细胞上的PD-1受体与其配体PD-L1之间的相互作用，从而恢复T细胞功能，增强T细胞对肿瘤细胞的杀伤能力^[7-8]。然而过度激活的T细胞可以引起自身免疫介导的不良反应，对机体各系统组织产生免疫性损伤，称之为irAE。本研究分析了同济大学附属上海市肺科医院使用单药PD-1抑制剂免疫治疗的irAE发

生情况, 以及irAE的发生与疗效的相关性。

Pillai等^[9]对晚期NSCLC行PD-1抑制剂治疗的12个研究共3 284例患者的irAE进行了meta分析, 疲乏为最常见的irAE, 发生率为19%, 甲状腺功能减退发生率为6.7%, 皮疹及腹泻发生率为9%, 免疫性肺炎为4%, 结肠炎、便秘、血液学毒性、免疫性肝炎等少见。Remon等^[10]对晚期NSCLC患者PD-1抑制剂治疗irAE的发生进行了汇总, 最常见的irAE为疲乏(20%左右)和皮肤反应(20%~40%); 其次为免疫性肝炎、胃肠道反应、内分泌系统毒性等, 少见irAE包括免疫性肺炎(约5%)、心脏毒性(<1%)、神经毒性(3.0%~6.1%)、血液学毒性(约2%)、胰腺毒性(0.6%~3.0%)、肾毒性(2%~3%)、眼毒性(<1%)等, 并对常见irAE的发生时间进行了汇总, 不同irAE发生的时间不一样, 皮肤反应多发生于6.1周(0.1~100.0周), 胃肠道毒性为4.9周(0.1~91.0周), 内分泌系统毒性为12.2周(1.9~88.1周), 免疫性肝炎为8.7周(0.1~131.0周), 免疫性肺炎为30.3周(1.6~108.0周)。本研究中, 皮肤反应(25.7%)最常见, 其次为免疫性肝炎(16.6%)、疲乏(14.7%)、内分泌系统毒性(13.8%)等。irAE发生时间上, 皮疹反应为18.9周(0.2~38.5周), 瘙痒为28.5周(8.0~50.0周), 免疫性肝炎为27.1周(4.0~67.1周), 免疫性肺炎为28.2周(6.3~69.3周), 内分泌系统毒性为26.6周(4.0~40.0周), 消化系统毒性为6.1周(2.7~14.2周), 疲乏为24.0周(0.2~45.0周)等, 部分irAE发生时间比较长。本研究中, 免疫性肝炎、肺炎的发生率相对较高, 既往报道的数据多为临床研究数据的汇总分析, 患者PS评分较好, 而本研究包含了很多非临床研究患者, 多线治疗的患者相对较多, irAE发生率相对较高。另外, 中国为肝炎大国, 虽然乙肝病毒抗原阴性, 很多是慢性感染, 导致免疫性肝炎的发生率略高于既往报道, 可能是中国人群irAE谱中一个不一样的地方。本研究中3级以上irAE主要为免疫性肺炎, 免疫性肺炎是一种相对少见但危及生命的irAE。Fujimoto等^[11]回顾性分析

nivolumab治疗15个中心615例晚期NSCLC患者的真实世界数据, 10%的患者发生免疫性肺炎, 5%的患者出现3级及以上免疫性肺炎。Nishino等^[12]对包括黑色素瘤、NSCLC、肾癌等共4 496例患者使用PD-1抑制剂治疗后免疫性肺炎的发生进行meta分析, 总人群发生率为2.7%, 3级及以上肺炎发生率为0.8%, 肺癌与黑色素瘤相比肺炎发生率为4.1% vs 1.6%, 3级及以上肺炎发生率为1.8% vs 0.2% ($P<0.001$)。提示肺癌免疫性肺炎发生率高于黑色素瘤等其他肿瘤, 可能因为肺癌患者常暴露于吸烟和一些慢性肺损伤性疾病中, 如慢性阻塞性肺部疾病等, 导致免疫性肺炎发生率明显升高^[13]。3级肺炎发生率高于相关临床研究, 其可能原因: ① 中国很多肺癌患者为老年男性, 长期吸烟, 合并慢性支气管炎、慢性阻塞性肺病、甚至是陈旧性肺结核等慢性肺部疾病, 导致免疫性肺炎发生率升高。② 本研究人群包含较多非临床研究患者, 后线治疗者较多, 更能反应真实世界中肺炎发生率的情况。

本研究深入探索了irAE的发生与免疫治疗效果的相关性, 发现irAE组患者免疫治疗效果明显优于非irAE组, 多因素分析提示, 皮肤irAE者较非皮肤irAE者预后好。Ricciuti等^[14]回顾性分析了195例晚期NSCLC患者使用抗PD-1治疗的效果及与irAE发生率的关系, irAE组和非irAE组中位PFS分别为5.7和2.0个月($HR=0.41$, 95% CI: 0.30~0.57, $P<0.000 1$)。Ali等^[15]回顾性分析了40例使用nivolumab治疗的晚期NSCLC患者, 发现皮肤irAE组和非皮肤irAE组ORR分别为42%和7%。Haratani等^[16]回顾性分析了134例使用nivolumab治疗的晚期NSCLC患者的预后, 发现有irAE组效果更好, 中位PFS分别为9.2和4.8个月($P=0.04$)。然而, 目前irAE与免疫疗效之间的机制尚未阐明, 先前有研究^[17-18]表明, 黑色素瘤患者治疗后容易出现白癜风, 可能与黑色素瘤和正常黑色素细胞之间的共享抗原有关。NSCLC中皮肤irAE与疗效相关是否与共同抗原有关, 尚待进一步研究。

本研究分析了中国晚期NSCLC患者使用单药PD-1抑制剂后irAE的发生情况、发生时间、处理

及转归,探讨了irAE与免疫治疗效果的相关性,相较于国外临床研究数据,因中国人群既往的疾病谱与国外有所不同,同时本研究人群包含了使用BGB-A317、SHR1210、IBI308等国产PD-1单抗的患者等,本研究数据能更好地反映中国人群使用PD-1抑制剂的安全性和irAE发生率及与疗效的相关性等情况,数据更真实可靠。本研究也存在一定的局限性及不足,首先在非irAE组患者中,二线及后线以上治疗患者较irAE组偏多,这有可能令疗效评估出现偏倚,其次病例数不够多,尚待大样本研究进一步证实。

本研究发现肺癌患者PD-1单抗治疗后irAE多发生于6~27周,多为1~2级,皮肤irAE最多见,3~4级irAE多为免疫性肺炎,irAE发生与疗效相关,irAE患者相较于非irAE患者是否有着更好的疗效,irAE发生的机制以及有无预测irAE的标志物,尚需进一步研究探索。

[参 考 文 献]

- [1] BRAY F, FERLAY J, SOERJOMATARAM I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. *CA Cancer J Clin*, 2018, 68(6): 394-424.
- [2] CHEN W, SUN K, ZHENG R, et al. Cancer incidence and mortality in China, 2014 [J]. *Chin J Cancer Res*, 2018, 30(1): 1-12.
- [3] BORGHAEI H, PAZ-ARES L, HORN L, et al. Nivolumab versus docetaxel in advanced non-squamous non-small cell lung cancer [J]. *N Engl J Med*, 2015, 373(17): 1627-1639.
- [4] BRAHMER J, RECKAMP K L, BAAS P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small cell lung cancer [J]. *N Engl J Med*, 2015, 373(2): 123-135.
- [5] HERBST R S, BAAS P, KIM D W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small cell lung cancer (KEYNOTE-010): a randomised controlled trial [J]. *Lancet*, 2016, 387(10027): 1540-1550.
- [6] MOK T S, WU Y L, KUDABA I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial [J]. *Lancet*, 2019, 393(10183): 1819-1830.
- [7] TOPALIAN S L, HODI F S, BRAHMER J R, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer [J]. *N Engl J Med*, 2012, 366(26): 2443-2454.
- [8] PARDOLL D M. The blockade of immune checkpoints in cancer immunotherapy [J]. *Nat Rev Cancer*, 2012, 12(4): 252-264.
- [9] PILLAI R N, BEHERA M, OWONIKOKO T K, et al. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: a systematic analysis of the literature [J]. *Cancer*, 2018, 124(2): 271-277.
- [10] REMON J, MEZQUITA L, CORRAL J, et al. Immune-related adverse events with immune checkpoint inhibitors in thoracic malignancies: focusing on non-small cell lung cancer patients [J]. *J Thorac Dis*, 2018, 10(Suppl 13): S1516-S1533.
- [11] FUJIMOTO D, YOSHIOKA H, KATAOKA Y, et al. Efficacy and safety of nivolumab in previously treated patients with non-small cell lung cancer: a multicenter retrospective cohort study [J]. *Lung Cancer*, 2018, 119: 14-20.
- [12] NISHINO M, GIOBBIE-HURDER A, HATABU H, et al. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis [J]. *JAMA Oncol*, 2016, 2(12): 1607-1616.
- [13] TOH C, WONG E, LIM W, et al. The impact of smoking status on the behavior and survival outcome of patients with advanced non-small cell lung cancer: a retrospective analysis [J]. *Chest*, 2004, 126(6): 1750-1756.
- [14] RICCIUTI B, GENOVA C, DE G A, et al. Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis [J]. *J Cancer Res Clin Oncol*, 2019, 145(2): 479-485.
- [15] ALI O H, DIEM S, MARKERT E, et al. Characterization of nivolumab-associated skin reactions in patients with metastatic non-small cell lung cancer [J]. *Oncoimmunology*, 2016, 5(11): e1231292.
- [16] HARATANI K, HAYASHI H, CHIBA Y, et al. Association of immune-related adverse events with nivolumab efficacy in non-small cell lung cancer [J]. *JAMA Oncol*, 2018, 4(3): 374-378.
- [17] TEULINGS H E, LIMPENS J, JANSEN S N, et al. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis [J]. *J Clin Oncol*, 2015, 33(7): 773-781.
- [18] HUA C, BOUSSEMART L, MATEUS C, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab [J]. *JAMA Dermatol*, 2016, 152(1): 45-51.

(收稿日期: 2020-06-05 修回日期: 2021-07-20)