Journal of Chinese Oncology,2021,Vol.27,No.9

免疫检查点抑制剂联合抗血管生成药物治疗晚期非小细胞肺癌的临床疗效与安全性

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摘　要:[目的] 探讨免疫检查点抑制剂(immune checkpoint inhibitors,ICIs)联合抗血管生成药物在晚期非小细胞肺癌(non-small cell lung cancer,NSCLC)患者治疗中的疗效及安全性。[方法] 收集 61 例符合条件的晚期 NSCLC 患者,观察其客观缓解率(objective response,ORR)、无进展生存期(progression-free survival,PFS)及不良反应等。[结果] 纳入研究患者 ORR 为 45.9%,中位 PFS 为 7.9 个月(95%CI:6.38~9.41)。亚组分析显示,与后线治疗组相比,一线治疗组患者不仅 ORR 具有显著性差异(χ^2=9.300,P=0.010),PFS 也得到了显著性改善(χ^2=8.993,P=0.011)。联合化疗组患者与未联合化疗组患者相比,ORR 和 PFS 均无统计学差异(ORR:χ^2=0.006,P=0.939;PFS:χ^2=0.350,P=0.554)。联合化疗组血液毒性及消化道不良反应的发生率显著性高于未联合化疗组(χ^2=4.725,P=0.030;χ^2=4.750,P=0.029)。ICIs 联合不同种类的抗血管生成药物的 PFS 无显著性差异 (χ^2=2.258,P=0.323)。 [结论] ICIs 联合抗血管生成药物治疗晚期 NSCLC 具有较好的疗效,且耐受性可。临床实践中,ICIs 前线联合抗血管生成药物患者获益可能更加明显,且无论联合哪类抗血管生成药物均能延长患者 PFS。联合化疗对患者 PFS 并无显著性改善,这为晚期 NSCLC 患者"去化疗"带来了新的希望。

主题词:非小细胞肺癌;免疫检查点抑制剂;抗血管生成;疗效
中图分类号:R734.2　　**文献标识码**:A　　**文章编号**:1671-170X(2021)09-0716-06
doi:10.11735/j.issn.1671-170X.2021.09.B004

Efficacy and Safety of Immune Checkpoint Inhibitors Combined with Anti-angiogenesis Therapy for Patients with Advanced Non-small Cell Lung Cancer

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Abstract:[Objective] To explore the efficacy and safety of immune checkpoint inhibitors(ICIs) combined with anti-angiogenesis therapy for patients with advanced non-small cell lung cancer(NSCLC). [Methods] The objective response rate (ORR), progression-free survival (PFS) and adverse events were observed in 61 eligible patients with advanced NSCLC. [Results] The ORR was 45.9%, and the median PFS was 7.9 months(95% CI:6.38~9.41). The subgroup analysis revealed a significant difference in ORR (χ^2=9.300, P=0.010) and PFS (χ^2=8.993, P=0.011) for patients receiving first-line treatment vs other lines. There was no significant difference in ORR (χ^2=0.006, P=0.939) and PFS (χ^2=0.350, P=0.554) between the combined chemotherapy group and the non-combined chemotherapy group. However, the incidence of blood toxicity and gastrointestinal side effects in the combined chemotherapy group was significantly higher than that in the non-combined chemotherapy group(χ^2=4.725, P=0.030; χ^2=4.750, P=0.029). In addition, there was no significant difference in PFS among patients receiving ICIs combined with different kinds of anti-angiogenic drugs (χ^2=2.258, P=0.323). [Conclusion] Immune checkpoint inhibitors combined with anti-angiogenic drugs in the treatment of advanced NSCLC has good efficacy with mild side effects. The patients with front-line ICIs combined with anti-angiogenic drugs may benefit more significantly, and no matter which type of anti-angiogenic drugs are combined, they can prolong PFS. In addition, we also found that combined chemotherapy did not significantly improve the PFS, which brings new hope for patients with advanced NSCLC to "de-chemotherapy".

Subject words: non-small cell lung cancer; immune checkpoint inhibitors; anti-angiogenesis; efficacy

近年来,免疫检查点抑制剂(immune checkpoint inhibitors,ICIs) 的出现为晚期非小细胞肺癌(non-small cell lung cancer,NSCLC)) 患者的治疗模式带来了全新突破[1]。CheckMate 017 和 CheckMate 057 研究发现,与多西他赛相比,纳武利尤单抗能显著性

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收稿日期:2021-06-30;**修回日期**:2021-07-25

延长鳞癌和非鳞癌患者的中位生存期（overall survival，OS）[2-3]。KEYNOTE 024 和KEYNOTE 042 Ⅲ期试验报道，与标准一线铂类化疗相比，使用帕博利珠单抗可显著性改善 NSCLC 患者的无进展生存期（progression-free survival，PFS）和 OS[4-5]。基于这些临床试验，程序性细胞死亡蛋白 1（programmed cell death 1，PD-1）抑制剂，包括纳武利尤单抗和帕博利珠单抗，现已被批准为 NSCLC 患者的标准治疗药物。然而，由于原发性耐药和获得性耐药，单药 ICIs 治疗疗效有限[6-7]。因此，我们尝试探索免疫治疗与其他药物联合使用的可能性。抗血管生成药物可以改善肿瘤组织的免疫微环境，从而提高免疫治疗的疗效，与 ICIs 具有潜在协同作用机制[8-10]。在一项多队列 Ⅰa/b 期临床试验中，帕博利珠单抗联合雷莫芦单抗对既往治疗过的晚期 NSCLC 患者产生了良好的抗肿瘤效应和可管理的安全性，为联合用药的有效性和安全性提供了证据[11]。我们进行了一项回顾性的临床数据分析，评估了 ICIs 联合抗血管生成治疗在真实世界中的安全性和有效性，并初步确定了联合治疗的最佳时机和模式。

1 资料与方法

1.1 一般资料

收集武汉大学人民医院肿瘤中心 2019 年 1 月至 2020 年 12 月期间收治的晚期 NSCLC 患者，共 61 例。患者随访采用电话随访，末次随访时间为 2021 年 6 月 30 日，中位随访时间 12.7 个月。患者纳入标准：(1)病理组织学明确诊断为 NSCLC；(2)TNM 分期Ⅲb~Ⅳ 期；(3)接受 PD-1 抑制剂联合抗血管生成药物治疗；(4)至少接受 2 个周期的 PD-1 抑制剂联合抗血管治疗(21 d 为 1 个周期)。

1.2 治疗方案

ICIs 均为 PD-1 抑制剂，包括帕博利珠单抗、纳武利尤单抗、信迪利单抗、特瑞普利单抗、卡瑞利珠单抗和替雷利珠单抗。抗血管生成药物包括大分子抗体类、小分子酪氨酸激酶抑制剂（tyrosine kinase inhibitors，TKI）类和内源性蛋白类三种，其中大分子抗体类均为贝伐珠单抗，小分子 TKI 类有安罗替尼、阿帕替尼和仑伐替尼，内源性蛋白类均为恩度。

化疗方案有紫杉醇联合奈达铂或卡铂、白蛋白紫杉醇联合奈达铂、培美曲塞联合奈达铂和多西他赛联合奈达铂。具体给药剂量为：紫杉醇 135 mg/m^2、培美曲塞 500 mg/m^2、白蛋白紫杉醇 260 mg/m^2、多西他赛 75 mg/m^2、奈达铂 75 mg/m^2、卡铂 1 000 mg/m^2，均为静脉滴注，每 21 d 重复。

1.3 观察指标

根据 RECIST 1.1[12]疗效评价标准对 ICIs 联合抗血管生成治疗的临床疗效进行评估：完全缓解（complete response，CR）：所有靶病灶消失；部分缓解（partial response，PR）：目标病灶直径之和至少减少 30%；疾病进展（progressive disease，PD）：靶病灶的直径之和至少增加 20%；疾病稳定（stable disease，SD）：疗效评价介于 PR 和 PD 之间。客观有效率（objective response rate，ORR）=(CR+PR)/总例数×100%。

无进展生存期（progression-free survival，PFS）定义为从接受 ICIs 联合抗血管生成治疗开始到疾病进展或患者死亡的时间。采用世界卫生组织不良反应评价标准对治疗不良反应进行评估。

肿瘤细胞的程序性死亡蛋白配体 1（programmed cell death ligand 1，PD-L1）的表达水平采用肿瘤细胞阳性比例分数（tumor proportion score，TPS)进行评分。

1.4 统计学处理

采用 SPSS 26.0 进行统计分析，Pearson 卡方检验或 Fisher 精确检验（当列联表中少于 5 个预期计数时)用于分析短期疗效与基线特征的关系。PFS 采用 Kaplan-Meier 法进行分析，组间差异用 Log-rank 检验进行比较。采用 Cox 回归模型进行多因素分析评估预后因素的作用。$P<0.05$ 为差异有统计学意义。使用 GraphPad Prism 8.0 绘制生存曲线。

2 结 果

共 61 例 NSCLC 患者纳入了这项真实世界的回顾性临床研究。入组患者临床资料完整，纳入患者主要为男性(78.7%)、年龄 < 65 岁(50.8%)、病理类型为腺癌（70.5%）、功能状态评分（performance status，PS)0~1 分(77.0%)、三线及以上使用 ICIs 联合抗血管治疗(42.6%)的晚期 NSCLC 患者。联合化疗组与未联合化疗组在性别、年龄、病理类型、EGFR 突变状态等方面差异均无统计学意义(Table 1)。纳入病

理类型、PS 评分、TPS 评分以及突变状态等进行多因素 Cox 回归分析显示，治疗线数是影响患者 PFS 的独立的影响因素(Table 2)。

2.1 疗效分析

2.1.1 短期疗效

在 61 例接受 ICIs 联合抗血管生成治疗的 NSCLC 患者中，CR 2 例，PR 26 例，SD 29 例，PD 4 例，ORR 为 45.9%。按治疗线数分层进行亚组分析，接受一线治疗的患者 ORR 为 73.7%，均优于其他线治疗组，且 ORR 差异具有统计学意义(χ^2=9.300，P=0.010)。按治疗模式分层进行亚组分析，联合化疗组和未联合组患者的 ORR 分别为 45.5%、46.4%，差异无统计学意义(χ^2=0.006，P=0.939)(Table 3)。

2.1.2 无进展生存期

入组患者中位 PFS 为 7.9 个月(95%CI：6.38~9.41)(Figure 1)。治疗线数亚组分析显示，一线治疗患者 PFS 优于二线（10.0 个月 vs 7.9 个月)，优于三线及以上(10.0 个月 vs 6.2 个月)，差异具有统计学意义(χ^2=8.993，P=0.011)(Figure 2)。治疗模式分析显示，联合化疗组中位 PFS 为 8.3 个月(95%CI：6.194~10.406)，未联合化疗组中位 PFS 为 6.9 个月(95% CI：3.612~10.188)，差异无统计学意

Table 1 Characteristics of patients[n(%)]

Characteristic	N	Combined chemotherapy	Non-combined chemotherapy	χ^2	P
Gender				3.621	0.057
Male	48	29(87.9)	19(67.9)		
Female	13	4(12.1)	9(32.1)		
Age(years old)				0.399	0.527
≥65	30	15(45.5)	15(53.6)		
< 65	31	18(54.5)	13(46.4)		
Histology				3.611	0.177
Adenocarcinoma	43	24(72.7)	19(67.9)		
Squamous cell carcinomas	8	6(18.2)	2(7.1)		
Other	10	3(9.1)	7(25.0)		
Disease stage at diagnosis				2.104	0.147
Ⅲ	10	8(24.2)	2(7.1)		
Ⅳ	51	25(75.8)	26(92.9)		
PS score				0.123	0.726
0~1	47	26(78.8)	21(75.0)		
≥2	14	7(21.2)	7(25.0)		
PD-L1 TPS				1.322	0.834
≥50%	6	4(12.1)	2(7.1)		
1%~49%	8	5(15.2)	3(10.7)		
< 1%	8	5(15.2)	3(10.7)		
Unknown	39	19(57.6)	20(71.4)		
EGFR mutation status				1.726	0.422
Negative	20	9(27.3)	11(39.3)		
Positive	10	7(21.2)	3(10.7)		
Unknown	31	17(51.5)	14(50.0)		
Line of therapy				0.219	0.896
1	19	11(33.3)	8(28.6)		
2	16	8(24.2)	8(28.6)		
≥3	26	14(42.4)	12(42.9)		
Class of anti-angiogenic drugs				5.055	0.080
Large molecules	22	14(42.4)	8(28.6)		
Small molecules	31	13(39.4)	18(64.3)		
Endogenous protein	8	6(18.2)	2(7.1)		

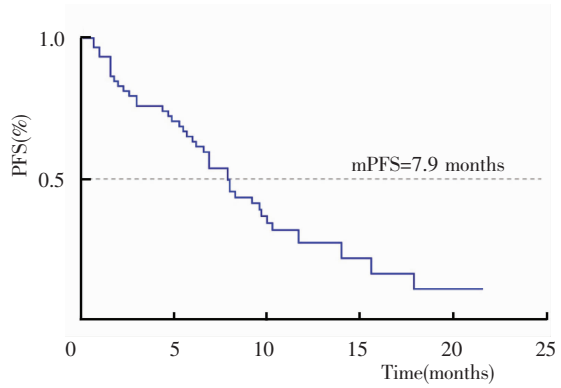

Figure 1 Survival curve of PFS in 61 patients

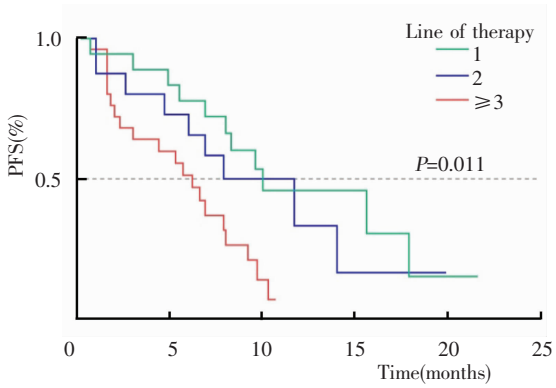

Figure 2 Survival curves of PFS in different lines of therapy

义(χ^2=0.350,P=0.554)(Figure 3)。按抗血管药物种类分层进行亚组分析,ICIs 联合三类抗血管生成药物治疗 NSCLC 的 PFS 无统计学差异(χ^2=2.258,P=0.323)(Figure 4)。可见 ICIs 无论联合哪种抗血管生成药物,均能使患者生存获益。

Table 2　Cox regression multivariate analysis of PFS

Variable	HR	95%CI	P
Histology			0.781
Adenocarcinoma	1.000		
Squamous cell carcinomas	0.680	0.166~2.786	0.592
Other	0.742	0.276~1.994	0.554
PS score	1.411	0.594~3.352	0.436
PD-L1 TPS			0.577
≥50%	1.000		
1%~49%	1.788	0.289~11.076	0.532
< 1%	1.242	0.234~6.599	0.799
Unknown	2.159	0.583~7.990	0.249
EGFR mutation status			0.125
Negative	1.000		
Positive	3.403	1.029~11.256	0.045
Unknown	1.652	0.682~4.002	0.266
Line of therapy			0.290
1	1.000		
2	1.488	0.541~4.093	0.442
≥3	3.576	1.305~9.802	0.013
Treatment pattern	0.546	0.193~1.545	0.254
Class of anti-angiogenic drugs			0.283
Large molecules	1.000		
Small molecules	0.477	0.172~1.326	0.156
Endogenous protein	0.467	0.119~1.835	0.275

Table 3　Short-term efficacy evaluation in different subgroups[n(%)]

Group	CR	PR	SD	PD	ORR
Total	2(3.3)	26(42.6)	29(47.5)	4(6.6)	28(45.9)
Line of therapy					
1	2(10.5)	12(63.2)	5(26.3)	0	14(73.7)
2	0	4(25.0)	9(56.3)	3(18.7)	4(25.0)
≥3	0	10(38.5)	15(57.7)	1(3.8)	10(38.5)
Treatment pattern					
ICIs+Anti-angiogenesis	2(7.1)	11(39.3)	12(42.9)	3(10.7)	23(46.4)
ICIs+Anti-angiogenesis+Chemotherapy	0	15(45.5)	17(51.5)	1(3.0)	32(45.5)

2.2　安全性分析

最常见的不良反应为血液性毒性(50.8%)和乏力(44.3%)。皮疹(4.9%)及免疫性肺炎(3.3%)的发生相对少见,肝肾毒性可控。患者血液毒性主要包括三系细胞减少和出血等。消化道不良反应包括恶心呕吐、腹泻等。亚组分析显示,联合化疗组骨髓抑制、恶心呕吐的发生率要明显高于未联合化疗组(χ^2=4.725,P=0.030;χ^2=4.750,P=0.029)(Table 4)。未发现与治疗相关导致死亡或停药的不良事件。

3　讨　论

免疫疗法为肿瘤治疗带来了新的革命。晚期 NSCLC 患者的系统治疗已由传统化疗向靶向及免疫治疗转变[13]。ICIs 因其较化疗具有更持久的抗肿瘤效应和生存优势,已成为晚期NSCLC 的新标准治疗方法[14]。然而,免疫单药治疗的临床试验结果并没有达到预期结果[15-16]。近来,ICIs 联合抗血管生成治疗已经成为一种新的治疗模式。这种模式是基于抗血管生成药物不仅能逆转血管内皮生长因子(vascular endothelial growth factor, VEGF)导致的免疫抑制效应,同时促进了免疫效应细胞向肿瘤部位的转运,从而提高了免

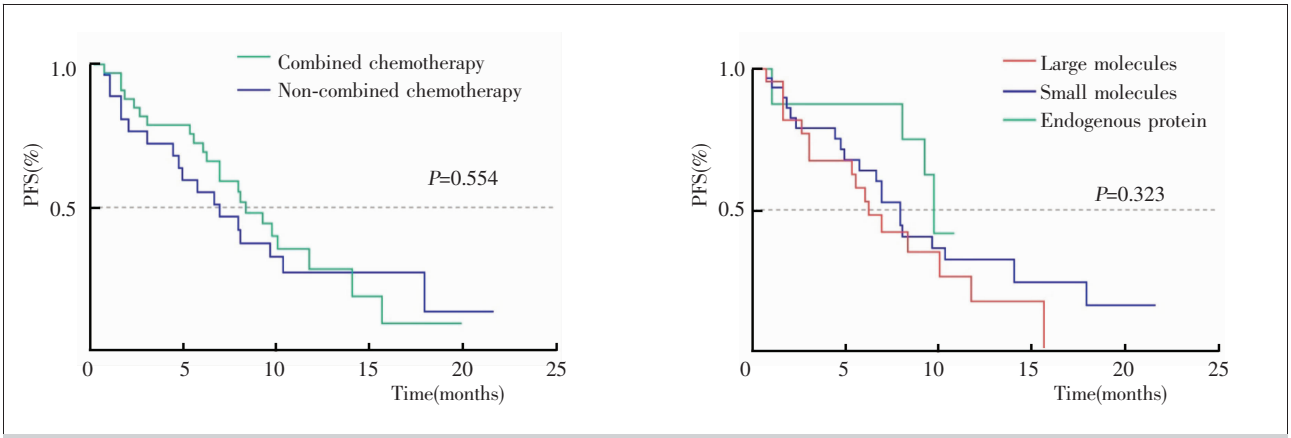

Figure 3　Survival curves of PFS in different treatment pattern

Figure 4　Survival curves of PFS in different anti-angiogenic drugs

Table 4 Safety analysis of combined chemotherapy group and non-combined chemotherapy group[n(%)]

Groups	N	Blood toxicity	Gastrointestinal reaction	Abnormal liver function	Abnormal renal function	Fatigue	Rash	Hypertension	Hand-foot syndrome	Pneumonia
Total	61	31(50.8)	17(27.9)	12(19.7)	18(29.5)	27(44.3)	3(4.9)	13(21.3)	9(14.8)	2(3.3)
Combined chemo therapy	33	21(63.6)	13(39.4)	6(18.2)	11(33.3)	16(48.5)	2(6.1)	5(15.2)	4(12.1)	1(3.0)
Non-combined chemo therapy	28	10(35.7)	4(14.3)	5(17.9)	7(25.0)	11(39.3)	1(3.6)	8(28.6)	5(17.9)	1(3.6)
P		0.030	0.029	0.585	0.526	0.193	1.000	0.182	0.719	1.000

疫治疗的疗效[17-18]。在 IMpower 150 研究中,阿特珠单抗联合贝伐珠单抗延长了患者 PFS 和 OS,为联合治疗的有效性提供了证据[19-20]。然而,有关免疫治疗联合抗血管生成治疗的真实世界数据仍然较少。因此,我们通过对临床数据进行回顾性分析来进一步探讨这一问题。

多项Ⅰ~Ⅱ期临床试验显示 ICIs 联合抗血管生成药物具有抗 NSCLC 活性。一项Ⅰb/Ⅱ期 KEYNOTE-524 研究的结果显示,帕博利珠单抗联合仑伐替尼后线治疗晚期 NSCLC 的 ORR 为 33.3%,中位 PFS 为 5.9 个月[21]。一项卡瑞利珠单抗联合阿帕替尼治疗既往接受过二线及以上化疗的晚期 NSCLC 的多中心 Ⅱ期临床研究结果报道,91 例患者的 ORR 为 30.8%,中位 PFS 为 5.9 个月[22]。本研究以真实世界临床数据进一步说明了免疫治疗联合抗血管生成治疗在晚期 NSCLC 患者中的疗效及安全性良好。在 ICIs 联合抗血管生成药物最佳使用时机方面,我们发现一线使用 ICIs 联合抗血管生成药物的患者,ORR 和 PFS 均显著性优于后线治疗组,且无论联合哪种抗血管生成药物,都能使患者生存获益,这对临床实践具有重要意义。此外,我们还发现联合化疗对患者 PFS 并无明显改善,这为一般状况较差、高龄、无法耐受化疗的晚期 NSCLC 患者打开了新的窗户。

VEGF 不仅能够诱导肿瘤新生血管形成直接促进肿瘤的生长和转移,还能通过诱导调节性 T 细胞增殖分化、下调淋巴细胞功能、抑制树突状细胞前体细胞成熟等机制导致肿瘤微环境形成免疫抑制[23-25]。抗血管生成药物使肿瘤血管正常化的同时,还可逆转免疫抑制,促进淋巴细胞和效应因子向肿瘤病灶运输[26-28]。另一方面,ICIs 不仅可以调节免疫微环境,还可以抑制异常肿瘤血管生成[29]。ICIs 通过激活免疫效应细胞分泌各种抗肿瘤细胞因子,发挥抗肿瘤新生血管生成、促进血管正常化的作用[30-31]。本研究以真实世界数据支持上述基础研究结果,提示 ICIs 联合抗血管药物治疗晚期 NSCLC 在临床实践中仍然是一个可行的选择。

本研究存在局限性:首先,本研究仅涉及一个中心,总体样本量以及亚组样本量有限;其次,各亚组配对无法完全平衡;再次,患者随访时间短,OS 尚不能用于分析。鉴于上述局限性,我们的结论可能需要更大的样本量来进一步证实。

综上,本研究探讨了 ICIs 联合抗血管生成药物治疗晚期 NSCLC 的应用。研究结果显示,ICIs 联合抗血管生成药物治疗晚期 NSCLC 在临床实践中是一种可行的治疗模式,前线联合患者临床获益可能更加显著,而且不受抗生血管生成药物种类的影响。另外,本研究还发现联合化疗对患者 PFS 无显著性改善,有望为晚期 NSCLC 患者“去化疗”打开新的篇章。

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