·临床研究·

放疗联合免疫治疗在晚期老年非小细胞肺癌患者中的应用价值

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【摘 要】 目的 分析放疗联合免疫治疗在晚期老年非小细胞肺癌(NSCLC)患者中的应用价值。**方法** 选取2018年1月至2023年8月凉山彝族自治州第一人民医院收治的206例晚期老年NSCLC患者为研究对象。根据治疗方案,将患者分为免疫治疗组[程序性细胞死亡受体1(PD-1)免疫检查点抑制剂治疗,$n=101$]及联合治疗组[PD-1抑制剂联合容积旋转调强放射治疗(VMAT),$n=105$]。比较两组患者临床疗效、治疗前后T细胞亚群($CD4^+$、$CD8^+$、$CD4^+/CD8^+$)、肺功能[第一秒用力呼气量(FEV1)、用力肺活量(FVC)、FEV1/FVC]及不良反应差异。采用SPSS 25.0统计软件进行数据分析。采用Kaplan-Meier生存曲线分析两组患者治疗后15个月无进展生存期(PFS)差异。**结果** 联合治疗组患者客观有效率(50.48%和35.64%)及疾病控制率(81.90%和69.31%)均高于免疫治疗组($P<0.05$)。两组患者治疗结束后$CD4^+$、$CD4^+/CD8^+$与FEV1、FVC、FEV1/FVC均较治疗前升高($P<0.05$),联合治疗组治疗后上述指标均高于免疫治疗组($P<0.05$)。两组患者治疗不良反应发生率比较,差异均无统计学意义(均$P>0.05$)。以治疗15个月为终点,联合治疗组与免疫治疗组疾病进展率分别为30.48%(32/105)及48.51%(49/101)。Kaplan-Meier曲线分析显示,联合治疗组PFS中位数为12.41个月(95%*CI* 11.564~13.255),显著高于免疫治疗组的10.56个月(95%*CI* 9.576~11.553),差异有统计学意义($\chi^2=7.465$,$P=0.006$)。**结论** VMAT联合PD-1抑制剂免疫治疗,不仅有助于提高晚期老年NSCLC患者临床疗效,且安全性良好,在改善患者免疫功能与肺功能、提升PFS方面均具有积极意义。

【关键词】 老年人;非小细胞肺癌;免疫治疗;放射治疗;容积旋转调强放射治疗;免疫检查点抑制剂;无进展生存期

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Application value of radiotherapy combined with immunotherapy in elderly patients with advanced non-small cell lung cancer

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【Abstract】 Objective To analyze the application value of radiotherapy combined with immunotherapy in elderly patients with advanced non-small cell lung cancer (NSCLC). **Methods** A total of 206 elderly patients with advanced NSCLC admitted to the First People's Hospital of Liangshan Yi Autonomous Prefecture from January 2018 to August 2023 were selected as the study subjects. According to the treatment regimens, the patients were divided into an immunotherapy group ($n=101$) treated with programmed cell death receptor 1 (PD-1) immune checkpoint inhibitors and a combination therapy group ($n=105$) treated with PD-1 inhibitors combined with volume rotation intensity modulated radiation therapy (VMAT). The two groups were compare in the clinical efficacy, T-cell subsets ($CD4^+$, $CD8^+$, $CD4^+/CD8^+$), pulmonary function [forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC] before and after treatment, and adverse reactions. SPSS 25.0 was used for data processing. Kaplan-Meier survival curves were used to analyze the difference in progression-free survival (PFS) at 15 months after the beginning of treatment in the two groups. **Results** The objective response rate (50.48% *vs* 35.64%) and disease control rate (81.90% *vs* 69.31%) in the combination therapy group were higher than those in the immunotherapy group ($P<0.05$). After the treatment, $CD4^+$, $CD4^+/CD8^+$, FEV1, FVC and FEV1/FVC in both groups increased as compared with before treatment ($P<0.05$), and the above indicators in the combination therapy group after treatment were higher than those in the immunotherapy group ($P<0.05$). With 15 months of treatment as the end point, the disease progression rate was 30.48% (32/105) in the combination therapy group and 48.51% (49/101) in the immunotherapy group. Kaplan-Meier curve analysis showed that the median PFS of the combination therapy group [12.41 months (95%*CI* 11.564-13.255)] was significantly longer than that of the immunotherapy group [10.56 months (95%*CI* 9.576-11.553)], and the difference was statistically significant (Log-rank $\chi^2=7.465$, $P=0.006$). **Conclusion** VMAT combined with PD-1 inhibitor immunotherapy not only helps enhance the clinical efficacy in elderly patients with advanced NSCLC with good safety but also has positive significance in improving immunity function and pulmonary function and increasing PFS.

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【Key words】 aged; non-small cell lung cancer; immunotherapy; radiotherapy; volume rotation intensity modulated radiation therapy; immune checkpoint inhibitor; progression free survival

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最新流行病学调查报告显示,2022 年全球肺癌新诊断病例为 250 万,死亡病例数则超过 180 万,是全球范围内患病率及病死率最高的恶性肿瘤[1]。非小细胞肺癌(non-small cell lung cancer, NSCLC)作为肺癌最常见的病理类型,老年人为主要患病人群,由于早期症状隐匿,NSCLC 确诊时常已处于中晚期,错失手术治疗时期,需行非手术抗肿瘤治疗[2]。对于驱动基因突变阴性的晚期 NSCLC 患者,程序性细胞死亡受体 1(programmed cell death receptor 1, PD-1)等免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)治疗可增强机体抗肿瘤免疫应答能力,延长晚期 NSCLC 患者生存期,但接受 ICIs 治疗的患者应答率存在差异,部分患者治疗效果不佳[3]。近年研究发现,容积旋转调强放射治疗(volume rotation intensity modulated radiation therapy, VMAT)等放疗与免疫治疗联合可发挥协同增效作用,为晚期 NSCLC 患者带来显著的临床获益[4]。但晚期老年 NSCLC 患者能否耐受放疗及其不良反应,联合放疗是否也能使老年患者获益,相关报道少见。基于此,本研究分析 VMAT 联合 PD-1 抑制剂治疗对晚期 NSCLC 老年患者的影响,以期为后续临床治疗提供参考数据。

1 对象与方法

1.1 研究对象

本文为回顾性单中心研究,选取 2018 年 1 月至 2023 年 8 月凉山彝族自治州第一人民医院收治的 206 例晚期老年 NSCLC 患者为研究对象。根据患者治疗方案,将其分为免疫治疗组 101 例(予 PD-1 抑制剂治疗)及联合治疗组 105 例(予 PD-1 抑制剂联合 VMAT 治疗)。纳入标准:(1)经纤维支气管镜或经皮穿刺肺组织活检病理学检查确诊为 NSCLC 中的鳞癌或腺癌;(2)影像学评估有可测量的目标病灶,且符合国际抗癌联盟第 8 版肺癌临床分期[5] Ⅲ~Ⅳ期;(3)年龄≥60 岁;(4)美国东部肿瘤协作组活动状态评分[6]为 0~1 分;(5)无明显器质性疾病或重要组织器官功能障碍;(6)无驱动基因突变;(7)影像学检查等资料完整。排除标准:(1)合并间质性肺疾病或入院前 1 年内肺炎患病史;(2)合并自身免疫性疾病或既往长期使用免疫抑制剂治疗;(3)合并精神分裂症等精神疾病;(4)合并其他恶性肿瘤;(5)合并梅毒等传染性疾病;(6)预计生存期不足 3 个月。

1.2 方法

1.2.1 治疗方法 免疫治疗组给予 ICIs 一线或高姑息治疗:鳞癌患者给予 PD-1 抑制剂帕博利珠单抗(批号:SJ20180019;规格:100 mg/4 ml;厂家:爱尔兰 MSD Ireland Carlow)2 mg/kg 或替雷利珠单抗(批号:S20190045;规格:100 mg/10 ml;厂家:广州百济神州生物制药有限公司)200 mg/3 w;腺癌患者给予 PD-1 抑制剂卡瑞利珠单抗(批号:S20190027;规格:200 mg;厂家:苏州盛迪亚生物医药有限公司)200 mg 或信迪利单抗(批号:S20180016;规格:100 mg/10 ml;厂家:苏州信达生物制药有限公司)200 mg/3 w。以 3 周为 1 个周期,连续治疗 4 个周期。联合治疗组在免疫治疗组基础上联合 VMAT:使用增强 CT 连续扫描,层厚 5 mm,扫描范围由下颌至肾上极,在窗宽 1600、窗位-600 的肺窗行肿瘤病灶靶区勾画,在窗宽 400、窗位 20 的纵膈窗行纵膈肿瘤病灶的勾画,放疗靶区包含增强 CT 可见的肿瘤组织及转移性肿大淋巴结,临床靶区为肿瘤靶区的基础上向外扩展(鳞癌外扩 6 mm、腺癌外扩 8 mm),以 95%等剂量曲线覆盖计划靶区,使用直线加速器 6MV-X(瑞典 Elekta)实施放疗,30-50 Gy/5-10 f。纵隔转移淋巴结在淋巴结靶区的基础上向外扩展 3 mm,常规分割,60 Gy/30 f/6 w。

1.2.2 疗效标准 治疗结束后,参考实体肿瘤的疗效评价标准 1.1 版[7],分为完全缓解(肿瘤病灶均消失)、部分缓解(靶病灶最长径+淋巴结最短径减少≥30%)、疾病稳定(介于部分缓解与疾病进展之间)、疾病进展(靶病灶最长径+淋巴结最短径增加≥20%或可见新病灶)。计算客观有效率(objective response rate, ORR)及疾病控制率(disease control rate, DCR),ORR=(完全缓解例数+部分缓解例数)/总治疗例数×100%,DCR=(完全缓解例数+部分缓解例数+稳定例数)/总治疗例数×100%。

1.2.3 观察指标 使用全自动流式细胞仪(日本 SYSMEX,型号 CyFlow Counter)检测 T 细胞亚群 $CD4^+$、$CD8^+$、$CD4^+/CD8^+$。使用肺功能检测仪(日本 CHEST,型号 HI-101)检测第一秒用力呼气量(forced expiratory volume in one second, FEV1)、用力肺活量(forced vital capacity, FVC)及 FEV1/FVC,评估肺功能。

1.2.4 不良反应 参考美国卫生及公共服务部常见不良反应事件评价标准 4.0 版[8]评估不良反应及

发生等级。

1.2.5 资料收集方法 经住院电子病历系统获取患者性别、年龄、病理类型、临床分期及既往史等基线资料。

1.2.6 预后观察 以电话随访及查阅电子病历的方式实施预后随访,以免疫治疗开始时为起点,治疗开始后15个月为终点。无进展生存期(progression-free survival, PFS)定义为免疫治疗开始至疾病进展或未进展但死亡的时间。

1.3 统计学处理

采用SPSS 25.0统计软件进行数据分析。符合正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,组间比较采用独立样本t检验,组内治疗前后比较采用配对样本t检验;计数资料以例数(百分率)表示,组间比较采用χ^2检验或Fisher精确概率法;等级资料采用Mann-Whitney U检验。采用Kaplan-Meier法绘制生存曲线,组间生存差异比较采用Log-rank检验。$P<0.05$为差异有统计学意义。

2 结 果

2.1 两组患者基线资料

联合治疗组与免疫治疗组基线资料比较,差异均无统计学意义($P>0.05$;表1)。

2.2 两组患者临床疗效

联合治疗组ORR及DCR显著高于免疫治疗组,差异均有统计学意义($P<0.05$;表2)。

2.3 两组患者T细胞亚群

治疗结束后,两组患者$CD4^+$及$CD4^+/CD8^+$均较治疗前升高($P<0.05$),联合治疗组治疗后$CD4^+$及$CD4^+/CD8^+$均高于免疫治疗组,差异均有统计学意义($P<0.05$;表3)。

2.4 两组患者肺功能

治疗结束后,两组患者FEV1、FVC及FEV1/FVC均较治疗前升高($P<0.05$),联合治疗组治疗后FEV1、FVC及FEV1/FVC均高于免疫治疗组($P<0.05$;表4)。

表1 两组患者基线资料比较

Table 1 Comparison of baseline data between two groups

Item	Combination therapy group($n=105$)	Immunotherapy group($n=101$)	χ^2/t	P value
Gender[n(%)]			0.044	0.834
Male	64(60.95)	63(62.38)		
Female	41(39.05)	38(37.62)		
Age(years, $\bar{x}\pm s$)	67.45±3.27	66.98±3.05		
Pathological type[n(%)]			0.218	0.640
Squamous cell carcinoma	59(56.19)	60(59.41)		
Adenocarcinoma	46(43.81)	41(40.59)		
Clinical staging[n(%)]			0.236	0.627
Stage Ⅲ	29(27.62)	31(30.69)		
Stage Ⅳ	76(72.38)	70(69.31)		
Activity status score[n(%)]			0.001	0.978
0 point	31(29.52)	30(29.70)		
1 point	74(70.48)	71(70.30)		
Family history of cancer[n(%)]	12(11.43)	10(9.90)	0.126	0.723
Smoking history[n(%)]	44(41.90)	41(40.59)	0.037	0.849

表2 两组患者临床疗效比较

Table 2 Comparison of clinical efficacy between two groups [n(%)]

Group	n	Complete response	Partial response	Stable disease	Progressive disease	ORR	DCR
Combination therapy	105	4(3.81)	49(46.67)	33(31.43)	19(18.10)	53(50.48)	86(81.90)
Immunotherapy	101	1(0.99)	35(34.65)	34(33.66)	31(30.69)	36(35.64)	70(69.31)
Z/χ^2			2.537			4.616	4.445
P value			0.011			0.032	0.035

ORR: objective response rate; DCR: disease control rate.

表3 两组患者$CD4^+$、$CD8^+$及$CD4^+/CD8^+$比较

Table 3 Comparison of $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ between two groups ($\bar{x}\pm s$)

Group	n	$CD4^+$(%)		$CD8^+$(%)		$CD4^+/CD8^+$	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination therapy	105	32.46±3.91	39.82±4.05*	24.12±3.22	23.09±3.19	1.32±0.22	1.71±0.33*
Immunotherapy	101	32.72±3.69	36.02±4.31*	24.48±2.97	23.21±3.35	1.33±0.23	1.57±0.34*
t		0.490	6.524	0.833	0.262	0.319	2.999
P value		0.624	<0.001	0.406	0.794	0.750	0.003

Compared with the same group before treatment, *$P<0.05$.

表 4 两组患者 FEV1、FVC 及 FEV1/FVC 比较

Table 4 Comparison of FEV1, FVC and FEV1/FVC between two groups ($\bar{x}\pm s$)

Group	n	FEV1(L)		FVC(L)		FEV1/FVC	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination therapy	105	1.25±0.22	2.23±0.39 *	2.72±0.55	3.46±0.63 *	0.46±0.09	0.67±0.12 *
Immunotherapy	101	1.29±0.25	2.04±0.40 *	2.80±0.57	3.27±0.61 *	0.47±0.08	0.63±0.14 *
t		1.220	3.452	1.025	2.196	0.842	2.204
P value		0.224	0.001	0.307	0.029	0.401	0.029

FEV1: forced expiratory volume in one second; FVC: forced vital capacity. Compared with the same group before treatment, * $P<0.05$.

2.5 两组患者不良反应

两组患者肺炎、贫血、肠炎、反应性皮肤毛细血管增生、皮疹、心肌炎、肝功能异常及甲状腺功能异常发生率比较,差异均无统计学意义($P>0.05$;表 5)。

表 5 两组患者不良反应比较

Table 5 Comparison of adverse reactions between two groups [n(%)]

Adverse reaction	Combination therapy group (n=105)	Immuno therapy group (n=101)	χ^2	P value
Pneumonia				
Grade 1-2	12(11.43)	9(8.91)	0.356	0.550
Grade 3-4	0(0.00)	0(0.00)	-	1.000 *
Anemia				
Grade 1-2	3(2.86)	2(1.98)	0.002	0.965
Grade 3-4	1(0.95)	0(0.00)	-	1.000 *
Enteritis				
Grade 1-2	4(3.81)	3(2.97)	0.003	0.958 #
Grade 3-4	0(0.00)	1(0.99)	-	1.000 *
RCCEP hyperplasia				
Grade 1-2	5(4.76)	3(2.97)	0.093	0.761 #
Grade 3-4	0(0.00)	0(0.00)	-	1.000 *
Skin rash				
Grade 1-2	9(8.57)	8(7.92)	0.029	0.865
Grade 3-4	1(0.95)	1(0.99)	0.467	0.495 #
Myocarditis				
Grade 1-2	3(2.86)	2(1.98)	0.002	0.965 #
Grade 3-4	0(0.00)	0(0.00)	-	1.000 *
Liver dysfunction				
Grade 1-2	3(2.86)	2(1.98)	0.002	0.965 #
Grade 3-4	0(0.00)	0(0.00)	-	1.000 *
Thyroid dysfunction				
Grade 1-2	6(5.71)	4(3.96)	0.068	0.794 #
Grade 3-4	0(0.00)	0(0.00)	-	1.000 *

RCCEP: reactive cutaneous capillary endothelial hyperplasia. * Fisher's exact probability test; # continuous correction *Chi*-square test. -: no datum.

2.6 PFS 观察

以治疗开始后 15 个月为终点,联合治疗组和免疫治疗组分别有 32 例(30.48%)和 49 例(48.51%)患者发生疾病进展。Kaplan-Meier 曲线分析显示,联合治疗组 PFS 中位数为 12.41 个月(95% *CI* 11.564~13.255)显著高于免疫治疗组 10.56 个月(95%*CI* 9.576~11.553),差异有统计学意义(χ^2 = 7.465, P = 0.006;图 1)。

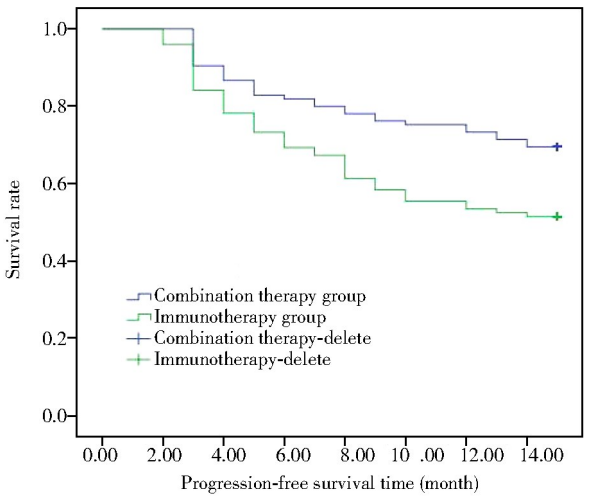


图 1 两组患者无进展生存期 Kaplan-Meier 曲线分析

Figure 1 Kaplan-Meier curve analysis of progression-free survival in two groups

3 讨 论

PD-1 抑制剂等 ICIs 治疗能阻断 NSCLC 等肿瘤细胞利用的免疫检查点,解除肿瘤细胞对 T 细胞的抑制作用,促使机体免疫系统恢复对肿瘤细胞的识别及杀伤能力,近年在晚期 NSCLC 治疗中常用[9]。但单一 ICIs 免疫治疗的应答率有限,部分患者疗效达不到预期,对此,有学者提出,将放疗与 ICIs 免疫治疗联合用于晚期 NSCLC,能达到较为理想的临床获益[10]。一方面,放疗能诱发 NSCLC 细胞死亡,提高局部控制率,并释放肿瘤抗原及炎症因子,激活宿主免疫应答[11];另一方面,ICIs 免疫治疗能放大放疗的免疫诱导效应,发挥协同增效作用,进一步提升疗效[12]。然而,晚期 NSCLC 具有较为显著的异质性,晚期老年 NSCLC 患者是否也能从放疗联合 ICIs 免疫治疗中获益,还需要进一步探究。

本研究发现,联合治疗组Ⅲ~Ⅳ期老年 NSCLC 患者治疗结束后 ORR 及 DCR 高于免疫治疗组,提示 PD-1 抑制剂联合 VMAT 可能提升Ⅲ~Ⅳ期老年 NSCLC 抗肿瘤效果,具有其优势。究其原因可能为 PD-1 抑制剂解除肿瘤免疫抑制状态,而放疗可被视为原位疫苗,进一步激活老年 NSCLC 患者免疫反应,从而联合 PD-1 抑制剂放大免疫诱导效应,

使晚期NSCLC整体治疗效果明显提升[13]。$CD4^+$不仅能促细胞免疫应答,还能使B淋巴细胞增殖,诱导特异性抗体生成,参与机体对肿瘤细胞的杀伤过程,$CD4^+/CD8^+$平衡变化是免疫治疗效果评价的重要工具,若该比值变大,提示机体免疫应答增强,肿瘤免疫逃逸可受到抑制[14]。观察两组免疫功能可发现,ICIs免疫治疗的两组在治疗结束后$CD4^+$、$CD4^+/CD8^+$均升高,而联合治疗组较免疫治疗组更高,也再次表明,VMAT联合ICIs免疫治疗能协同促进免疫诱导效应,提升疗效。

此外,ICIs免疫治疗与放疗对老年NSCLC的安全性,也是临床关注的焦点,ICIs及放疗均能引起肺炎等不良反应,联合治疗是否增加不良反应,导致安全性下降,值得重点关注[15,16]。本研究两组患者均未发生≥3级的肺炎及肝肾功能异常反应,组间不良反应比较差异也无统计学意义,提示联合VMAT并未增加不良反应,安全性良好。不仅如此,联合治疗组治疗后FEV1、FVC、FEV1/FVC高于免疫治疗组,提示联合治疗不仅并未增加肺炎等不良反应,还能提高抗肿瘤效果,促进老年NSCLC患者肺功能转归。

延长晚期老年NSCLC患者的PFS,被认为是改善预后、提升生存优势的关键[17]。本研究也发现,即使在相对较短的观察期内,即以治疗开始后15个月为终点,联合治疗组PFS也高于免疫治疗组,再次表明Ⅲ~Ⅳ期老年NSCLC患者能从VMAT联合ICIs免疫治疗中获益,PFS得到延长,更有利于预后生存。

综上,对于晚期老年NSCLC患者,VMAT联合PD-1抑制剂ICIs免疫治疗可能在提升抗肿瘤效果方面更具优势,同时在改善患者肺功能及免疫功能、提升PFS方面也具有一定优势,安全性尚可,值得临床推广应用。然而,本研究存在单中心、小样本量的局限性,导致结论代表性不足;且预后随访时间较短,因此上述结论仍需后续多中心、大样本量的长期随访研究进一步验证。

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