·临床研究·

纳武利尤单抗单药及联合安罗替尼治疗老年晚期胃癌患者的效果

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【摘 要】 **目的** 探讨纳武利尤单抗联合安罗替尼治疗老年晚期胃癌的效果。**方法** 选择徐州市肿瘤医院2021年1月至2023年1月收治的120例接受三线治疗的老年晚期胃癌患者为研究对象,其中60例患者接受纳武利尤单抗治疗(单药治疗组),另外60例患者接受纳武利尤单抗联合安罗替尼治疗(联合治疗组)。两组患者均连续治疗4个疗程,统计治疗后客观缓解率(ORR)及疾病控制率(DCR),检测治疗前后血管内皮生长因子A(VEGF-A)、癌胚蛋白(CEA)、基质金属蛋白酶-2(MMP-2)、基质金属蛋白酶-9(MMP-9)及外周血T淋巴细胞亚群水平,统计不良反应发生情况。采用SPSS 22.0统计软件进行数据分析,根据数据类型分别采用t检验或χ^2检验进行组间比较。采用Kaplan-Meier法分析各组病例累积生存率,采用Log-rank检验分析两组患者的生存差异性。**结果** 联合治疗组DCR及ORR分别为76.67%(46/60)和43.33%(26/60),均高于单药治疗组[58.33%(35/60)和25.00%(15/60)],差异均有统计学意义($P<0.05$)。联合治疗组治疗后血清VEGF-A、CEA、MMP-2及MMP-9水平均低于单药治疗组;$CD3^+$、$CD4^+$、$CD4^+/CD8^+$水平高于单药治疗组,$CD8^+$水平低于单药治疗组,差异均有统计学意义($P<0.05$)。联合治疗组与单药治疗组不良反应发生情况比较,差异无统计学意义($P>0.05$)。随访至2024年2月,结果显示联合治疗组及单药治疗组中位无进展生存时间(PFS)分别为6.10个月(95%*CI* 4.607~7.593)与4.00个月(95%*CI* 3.059~4.941);中位总生存时间(OS)分别为9.25个月(95%*CI* 8.394~10.099)与6.19个月(95%*CI* 5.583~6.789),差异均有统计学意义($\chi^2=6.298$、4.943,$P<0.05$)。**结论** 纳武利尤单抗联合安罗替尼作为老年晚期胃癌患者的三线治疗方案能有效延长患者生存时间,提高肿瘤控制效果,但其疗效需进一步开展多中心、大样本量的前瞻性研究进行验证。

【关键词】 老年人;晚期胃癌;安罗替尼;纳武利尤单抗;三线治疗
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Effect of nivolumab alone and combined with anlotinib in treatment of elderly patients with advanced gastric cancer

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【**Abstract**】 **Objective** To explore the effect of nivolumab combined with anlotinib in the treatment of elderly advanced gastric cancer. **Methods** A total of 120 elderly patients with advanced gastric cancer who received third-line treatment in our hospital from January 2021 to January 2023 were enrolled, and 60 of them received nivolumab treatment (single drug treatment group), and the other 60 ones received nivolumab combined with anlotinib treatment (combined treatment group). After four continuous courses of treatment, the objective remission rate (ORR) and disease control rate (DCR) were calculated. The peripheral blood levels of vascular endothelial growth factor A (VEGF-A), carcinoembryonic antigen (CEA), matrix metalloproteinase-2 (MMP-2) and MMP-9 and the percentages of peripheral blood T lymphocyte subsets were detected before and after treatment. The occurrence of adverse reactions was observed. SPSS statistics 22.0 was used for data analysis, and t test or *Chi*-square test was employed for between-group comparison depending on data type. Kaplan-Meier survival analysis was applied to analyze the cumulative survival rate of each group, and Log-rank test was conducted to analyze the difference in survival rate between the two groups. **Results** The DCR and ORR in the combined treatment group was 76.67% (46/60) and 43.33% (26/60), which were higher than those of the single drug treatment group [58.33% (35/60) and 25.00% (15/60), $P<0.05$]. After treatment, the combined treatment group had significantly lower serum VEGF-A, CEA, MMP-2 and MMP-9 levels, higher percentages of $CD3^+$, $CD4^+$ T cells and $CD4^+/CD8^+$ ratio, but lower percentage $CD8^+$ T cells when compared to the single drug treatment group ($P<0.05$). There was no statistical difference in occurrence of adverse reactions between the two groups ($P>0.05$). The patients were followed up until February 2024, and the results showed that in the combined treatment group and single drug treatment group, the median progression-free survival (PFS) was 6.10 months (95%*CI* 4.607-7.593) and 4.00 months (95%*CI*

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3.059-4.941), and the median overall survival (OS) was 9.25 months (95%*CI* 8.394-10.099) and 6.19 months (95%*CI* 5.583-6.789), respectively, with statistical differences between them (χ^2=6.298, 4.943, P<0.05). **Conclusion** Nivolumab combined with anlotinib, as a third-line treatment regimen, can effectively prolong the survival time and improve the tumor control effect in elderly patients with advanced gastric cancer. However, its efficacy needs to be further verified by multi-center, large-sample prospective studies.

【Key words】 aged; advanced gastric cancer; anlotinib; nivolumab; third-line treatment

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胃癌是临床上常见的消化系统恶性肿瘤,早期胃癌预后较好,但胃癌临床症状不典型,多数患者首次确诊时疾病已发展至晚期,而晚期胃癌的预后差,Ⅳ期胃癌年生存率往往低于10%[1]。部分晚期胃癌患者经一二线治疗后病情依旧进展,需接受进一步的抗肿瘤治疗,探讨晚期胃癌的后线治疗方案在临床中具有重要意义[2]。纳武利尤单抗是程序性死亡蛋白-1(programmed death-1,PD-1)抑制剂,该药物能增强T细胞功能,抑制癌细胞增殖与转移,中国临床肿瘤学会胃癌诊疗指南已将纳武利尤单抗三线治疗的推荐级别提升至最高[3]。安罗替尼是一种多靶点络氨酸激酶抑制剂(tyrosine kinase inhibitor,TKI),其具有抗血管生成及抑制肿瘤细胞增殖转移的双重功效[4]。随着临床研究的不断推进,抗血管生成治疗与免疫治疗相联合的"去化疗"模式逐渐应用于癌症晚期[5]。免疫药物的抗肿瘤功效与肿瘤微环境(tumor microenvironment,TME)中的免疫细胞浸润密切相关,而抗血管生成药物还能使TME从免疫抑制向免疫激活状态转变,故TKI联合PD-1抑制剂在理论上可发挥协同作用,增强抗肿瘤效果[6]。目前,关于安罗替尼联合纳武利尤单抗三线治疗晚期胃癌中的相关研究较少,本研究的开展为丰富晚期胃癌后线治疗方案提供了理论依据。

1 对象与方法

1.1 研究对象

选择徐州市肿瘤医院2021年1月至2023年1月收治的120例接受三线治疗的老年晚期胃癌患者为研究对象,根据治疗方案将患者分为单药治疗组(60例)与联合治疗组(60例)。纳入标准:(1)年龄≥60岁;(2)美国东部肿瘤协作组(Eastern Cooperative Oncology Group,ECOG)评分0~1分;(3)原发肿瘤-淋巴结-远处转移(tumor lymph node metastasis,TNM)分期Ⅲb期或Ⅳ期,不符合手术切除指征;(4)人类表皮生长因子受体2(human epidermal growth factor receptor-2,HER2)阴性;(5)经一线、二线常规标准治疗后无法耐受或病情进展/无明显缓解;(6)预计生存期>3个月。排除标准:(1)合并脑转移;(2)合并其他恶性肿瘤;(3)合并心、肝、肾等重要器官严重功能障碍;(4)既往胃部外科手术;(5)合并胃肠活动性出血;(6)在以往一二线治疗中使用过免疫检查点抑制剂或抗血管生成药;(7)对受试药物或其相关成分过敏。本研究经医院医学伦理委员会批准(伦理批号:20457),参与者均知情且签署知情同意书。

1.2 方法

1.2.1 治疗方法 单药治疗组患者使用纳武利尤单抗(宝时美施贵宝制药,国药准字:19010832,规格:100 mg/支)静脉滴注,用药剂量3 mg/kg,每两周1次。联合用药组在此基础上口服安罗替尼(正大天晴药业集团股份有限公司,国药准字:H20180002,规格:12 mg),每次12 mg,1次/d,连续服药14 d后停药7 d,再继续用药。每21 d为一个疗程,治疗4个疗程后观察疗效。

1.2.2 观察指标 (1)影像学检查。每2个疗程结束后进行一次影像学检查,参考《实体肿瘤疗效评价标准1.1版》[7]评价两组患者临床疗效。完全缓解(complete response,CR):全部癌灶直径缩小至10 mm以内;部分缓解(partial response,PR):全部癌灶直径缩小>30%;疾病稳定(stable disease,SD):介于完全缓解和部分缓解之间;疾病进展(progressive disease,PD):全部癌灶直径增大超20%或出现一个或以上新发病灶。疾病控制率(disease control rate,DCR)=(CR+PR+SD)/总例数×100%。客观缓解率(objective response rate,ORR)=(CR+PR)/总例数×100%。所有患者疗效评估均由相同的影像科医师及主治医师采用双盲法进行评估,两者意见不一致时经商议得出统一结论。(2)生物学指标及T细胞亚群水平检测。所有生物指标及T细胞亚群检查均由医院实验室使用统一仪器及试剂独立完成,外周血采集时间分别为治疗前2 d内及治疗4个疗程完成后2 d内,以确保测量的稳定性。生物学指标包括:血管内皮生长因子A(vascular endothelial growth factor-A,VEGF-A)、癌胚抗原(carcinoembryonic antigen,CEA)、基质金属蛋白酶-2(matrix metalloproteinase-2,MMP-2)、基质金属蛋白酶-9(matrix metalloproteinase-9,MMP-9)水平。采用流式细胞术检测外周血T淋巴细胞亚群,包括

$CD3^+$、$CD4^+$、$CD8^+$细胞占比,并计算 $CD4^+/CD8^+$。

1.2.3 不良反应 每个治疗周期结束后均进行血常规、生化、甲状腺、心电图等检查,评估不良反应发生情况。

1.2.4 随访 随访至 2024 年 2 月,统计两组患者疾病无进展生存期(progression-free survival,PFS)及总生存期(overall survival,OS)。

1.3 统计学处理

采用 SPSS 22.0 统计软件进行数据分析。计量资料以均数±标准差($\bar{x}\pm s$)表示,组间比较采用 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。PFS 及 OS 以月计算,以治疗日作为生存时间计算起点,疾病进展/死亡/截止随访时间为事件终点,通过寿命表法计算全组生存率,采用 Kaplan-Meier 法分析各组病例累积生存率,采用 Log-rank 检验分析两组患者的生存差异性。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 两组患者基线资料

两组患者性别、年龄、体质量指数等基线资料比较,差异均无统计学意义($P>0.05$;表 1)。

2.2 两组患者疗效

两组患者在治疗 4 个疗程后评估疗效,联合治疗组的 DCR 及 ORR 均高于单药治疗组,差异均有统计学意义($P<0.05$;表 2)。

2.3 两组患者治疗前后外周血生化指标水平

治疗后,两组患者血清 VEGF-A、CEA、MMP-2 及 MMP-9 水平均较治疗前下降;联合治疗组治疗后血清 VEGF-A、CEA、MMP-2 及 MMP-9 水平均低于单药治疗组,差异均有统计学意义($P<0.05$;表 3)。

2.4 两组患者治疗前后外周血 T 细胞亚群水平

治疗后,两组患者外周血 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平较治疗前升高,$CD8^+$ 水平均较治疗前下降;治疗后,联合治疗组患者 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平高于单药治疗组,$CD8^+$ 水平低于单药治疗组,差异均有统计学意义($P<0.05$;表 4)。

2.5 两组患者不良反应发生情况

两组患者骨髓抑制、消化道反应、高血压等不良反应发生情况比较,差异无统计学意义($P>0.05$;表 5)。

2.6 两组患者 PFS 及 OS 分析

随访至 2024 年 2 月,随访时间为 2~14 个月,中位随访时间为 6.80 个月,其中联合治疗组失访 5 例,单药治疗组失访 4 例。联合治疗组患者疾病 PFS 为 6.10 个月(95%*CI* 4.607~7.593),单药治疗组疾病 PFS 为 4.00 个月(95%*CI* 3.059~4.941),联合治疗组 PFS 高于单药治疗组,差异有统计学意义($\chi^2=6.298$,$P=0.012$;图 1)。联合治疗组患者 OS 为 9.25 个月(95%*CI* 8.394~10.099),单药治疗组 OS 为 6.19 个月(95%*CI* 5.583~6.789),差异有统计学意义($\chi^2=4.943$,$P=0.026$;图 2)。

表 1 两组患者基线资料比较

Table 1 Comparison of baseline data between two groups ($n=60$)

Item	Single drug treatment group	Combined treatment group	t/χ^2	P value
Gender[n(%)]			0.154	0.695
Male	42(70.00)	40(66.67)		
Female	18(30.00)	20(33.33)		
Age(years, $\bar{x}\pm s$)	65.45±3.15	66.11±4.05	0.996	0.321
Body mass index(kg/m^2, $\bar{x}\pm s$)	18.45±1.98	19.03±2.11	1.553	0.123
TNM staging[n(%)]			0.342	0.559
Ⅲb	39(65.00)	42(70.00)		
Ⅳ	21(35.00)	18(30.00)		
Differentiation degree[n(%)]			0.188	0.910
Low	10(16.67)	11(18.33)		
Middle-to-high	33(55.00)	34(56.67)		
Unknown	17(28.33)	15(25.00)		
Metastasis to other organs[n(%)]	40(66.67)	38(63.33)	0.147	0.702
Primary tumor site[n(%)]			0.069	0.996
Gastric fundus+gastric body	23(38.33)	24(40.00)		
Gastric antrum	26(43.33)	26(43.33)		
Unknown	11(18.33)	10(16.67)		

TNM: tumor lymph node metastasis.

表2 两组患者疗效比较

Table 2 Comparison of therapeutic efficacy between two groups [$n=60$, n(%)]

Group	CR	PR	SD	PD	DCR	ORR
Combined treatment	0(0.00)	26(43.33)	20(33.33)	14(23.33)	46(76.67)	26(43.33)
Single drug treatment	0(0.00)	15(25.00)	20(33.33)	25(41.67)	35(58.33)	15(25.00)
χ^2					4.596	4.483
P value					0.032	0.034

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; DCR: disease control rate; ORR: objective response rate.

表3 两组患者治疗前后外周血生化指标水平比较

Table 3 Comparison of peripheral blood biochemical indicators levels between two groups before and after treatment

($n=60$, $\bar{x}\pm s$)

Group	VEGF-A(ng/L)		CEA(ng/ml)		MMP-2(μg/L)		MMP-9(μg/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combined treatment	363.45±64.74	233.45±44.69*	23.97±6.48	10.66±2.21*	136.99±20.36	53.15±10.78*	487.77±76.59	203.74±61.17*
Single drug treatment	359.96±70.37	263.73±46.98*	24.53±5.49	15.34±2.41*	141.11±22.17	81.46±19.88*	493.04±77.89	336.46±60.36*
t	0.283	3.617	0.511	11.086	1.060	9.697	0.394	11.963
P value	0.778	<0.001	0.611	<0.001	0.291	<0.001	0.709	<0.001

VEGF-A: vascular endothelial growth factor-A; CEA: carcinoembryonic antigen; MMP-2: matrix metalloproteinase-2; MMP-9: matrix metalloproteinase-9. Compared with the same group before treatment, * $P<0.05$.

表4 两组患者治疗前后外周血T细胞亚群水平比较

Table 4 Comparison of peripheral blood T cell subsets between two groups before and after treatment ($n=60$, $\bar{x}\pm s$)

Group	$CD3^+$(%)		$CD4^+$(%)		$CD8^+$(%)		$CD4^+/CD8^+$	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combined treatment	27.46±4.15	49.66±8.47*	24.25±5.07	43.45±6.69*	25.97±4.98	17.61±3.66*	0.93±0.17	2.47±0.26*
Single drug treatment	28.01±4.63	40.42±7.79*	25.02±5.63	34.66±6.05*	26.15±5.17	20.66±4.06*	0.96±0.19	1.68±0.22*
t	0.685	6.220	0.787	7.549	0.194	4.322	0.911	17.967
P value	0.495	<0.001	0.433	<0.001	0.846	<0.001	0.364	<0.001

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

表5 两组患者不良反应发生情况比较

Table 5 Comparison of occurrence of adverse reactions between two groups [$n=60$, n(%)]

Group	Bone marrow suppression	Digestive tract reaction	Hypertension	Hypothyroidism	Oral mucositis	Fatigue	Abnormal liver function
Combined treatment	37(61.67)	26(43.33)	13(21.67)	10(16.67)	15(25.00)	30(50.00)	8(13.33)
Single drug treatment	32(53.33)	25(41.67)	19(31.67)	5(8.33)	11(18.33)	37(61.67)	6(10.00)
χ^2	0.853	0.034	1.534	1.905	0.786	1.656	0.324
P value	0.356	0.853	0.215	0.168	0.375	0.198	0.570

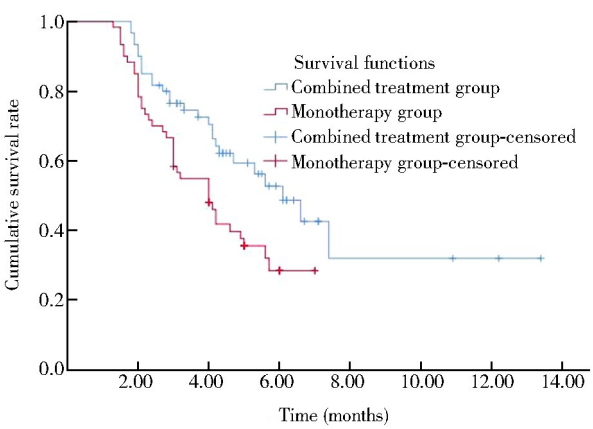


图1 两组患者PFS比较

Figure 1 Comparison between PFS between two groups

PFS: progression-free survival.

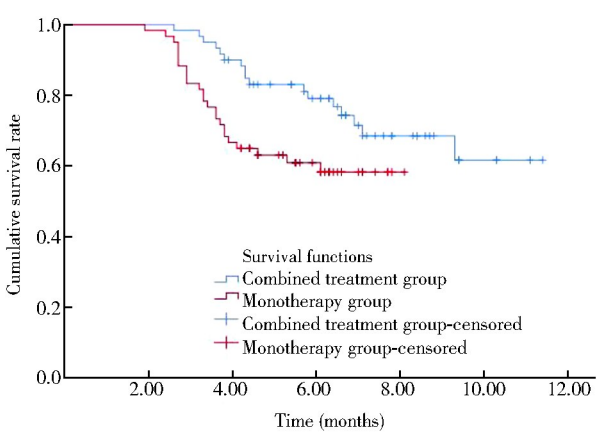


图2 两组患者OS比较

Figure 2 Comparison of OS between two groups

OS: overall survival.

3 讨 论

《胃癌治疗指南 2018》三线或更高线疗法中将纳武利尤单抗作为单独疗法的标准疗法[8]。Sugawara 等[9]研究表示,加用纳武利尤单抗治疗晚期肺癌患者 ORR 更高,且中位 PFS 显著延长。本研究中,单用纳武利尤单抗作为老年晚期胃癌患者的三线治疗方案,其中位 PFS 为 4 个月,与 Sugawara 等[9]研究结论相似。PFS 和 OS 是评估肿瘤治疗效果的"金标准",本研究结果显示,在纳武利尤单抗基础上加用安罗替尼的联合用药组患者中位 PFS 延长至 6.10 个月,且其中位 OS 也长于单药治疗组,且联合用药组 DCR 及 ORR 均更高,提示纳武利尤单抗联合安罗替尼可在一定程度上提高老年晚期胃癌患者三线治疗效果。

本研究结果显示,治疗后联合治疗组及单药治疗组外周血细胞因子 VEGF-A 水平均较同组治疗前明显下降;外周血 T 细胞亚群中 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$水平较同组治疗前升高,$CD8^+$水平均较同组治疗前下降,提示治疗后患者血管异常生成以及免疫抑制状态均得以缓解。但联合治疗组治疗后 VEGF-A 水平更低,外周血 T 细胞亚群中 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$水平更高,$CD8^+$水平更低,分析原因,可能与免疫抑制剂及抗血管生成药物在抗癌机制中可相互促进相关。有研究表示,抗血管生成药物能逆转 TME 中的免疫抑制状态,抑制血管异常化,而 PD-1 抑制剂的抗肿瘤效果与 TEM 中的免疫细胞浸润状态之间关系密切,在抗血管生成药物改善 TEM 免疫状态后,PD-1 抑制剂纳武利尤单抗的抗肿瘤效果增强[10,11]。此外,PD-1 抑制剂能有效调节 T 细胞功能,激活效应 T 细胞,上调抗肿瘤细胞因子分泌,而这些抗肿瘤细胞因子能作用于血管,进一步促进血管正常化,增强抗血管生成药物的作用效果[12,13]。以上研究说明联合纳武利尤单抗及安罗替尼能有效提高抗血管生成作用,解除免疫抑制。

此外,治疗后联合治疗组患者外周血 CEA、MMP-2 以及 MMP-9 水平也低于单药治疗组。CEA 是肿瘤细胞表面的结构抗原,是胃癌的血清标志物之一,MMP-2 及 MMP-9 在肿瘤细胞侵袭及转移中发挥重要作用,血清中 MMP-2 及 MMP-9 水平可反映肿瘤细胞侵袭及转移情况[14,15]。以上研究结果进一步从分子学角度证实经联合用药治疗后患者肿瘤控制效果更好。

此外,两组患者不良反应情况相比,差异无统计学意义,提示联合用药不增加安全性风险。但本研究所纳入的样本量较小,且为单中心研究,研究对象代表性不高,所得结论可能存在偏倚,后续可增大研究样本,开展前瞻性多中心研究,进一步探讨纳武利尤单抗联合安罗替尼在晚期胃癌三线治疗中的效果。

综上所述,纳武利尤单抗联合安罗替尼作为老年晚期胃癌患者的三线治疗方案能有效延长患者生存时间,提高肿瘤控制效果,但其疗效需进一步开展多中心、大样本量的前瞻性研究进行验证。

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