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贝伐单抗联合替莫唑胺对老年胶质母细胞瘤术后患者预后的影响*

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摘要 目的：探讨贝伐单抗联合替莫唑胺对老年胶质母细胞瘤术后患者预后的影响。**方法：**选择 2014 年 1 月到 2016 年 1 月在第四军医大学西京医院诊治的老年胶质母细胞瘤术后患者 78 例，根据治疗方法的不同分为观察组与对照组各 39 例，观察组给予替莫唑胺与贝伐单抗联合治疗，对照组只给予替莫唑胺治疗，观察和比较两组患者的的预后情况。**结果：**观察组与对照组的有效率分别为 48.7%和 23.1%，观察组显著高于对照组(P<0.05)。观察组治疗期间的肝肾反应、胃肠道反应、疲乏、骨髓抑制等毒副反应的发生率明显低于对照组 (P<0.05)。观察组治疗后的 KPS 与 ECOG 评分分别为 64.22± 2.19 分和 1.65± 0.45 分， 对照组为 56.35± 4.50 分和 2.41± 0.51 分，组间对比差异明显(P<0.05)，且与治疗前对比也有明显差异(P<0.05)。观察组与对照组的的中位生存时间分别为 30 个月和 21 个月，观察组的 3 年生存率为 41.0%，对照组为 16.4%，观察组都明显优于对照组(P<0.05)。**结论：**贝伐单抗联合替莫唑胺可显著改善老年胶质母细胞瘤术后患者的生存质量，提高治疗疗效与延长患者的生存时间，且安全性较高。

关键词：贝伐单抗；替莫唑胺；胶质母细胞瘤；毒副反应；预后

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Effect of Bevacizumab Combined with Temozolomide on the Prognosis of Elderly Postoperative Patients with Glioblastoma*

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ABSTRACT Objective: To investigate the effect of bevacizumab combined with temozolomide on the prognosis of elderly postoperative patients with glioblastoma. **Methods:** 78 elderly postoperative patients with glioblastoma in Xijing hospital from January 2014 to January 2016 were selected and equally divided into the observation group and control group with 39 patients in each group according to different methods of treatment. The observation group was treated by bevacizumab combined with temozolomide, while the control group was given temozolomide treatment, the clinical effect, survival time and quality and life as well as the incidence of adverse reactions were observed and compared between two groups of patients. **Results:** The effective rate of observation group and control group were 48.7% and 23.1% respectively, which was significantly higher in the observation group than that of the control group (P<0.05). During the treatment period, the incidence of liver and kidney dysfunction, gastrointestinal reaction, fatigue, bone marrow suppression and other toxic side effects in the treatment group were significantly lowed than those of the control group (P<0.05). The KPS and ECoG scores in the observation group after treatment were 64.22± 2.19 points and 1.65± 0.45 points, the control group were 56.35± 4.50 points and 2.41± 0.51 points, significant differences were observed between two groups (P<0.05). The median survival time was 30 months and 21 months in the observation group and control group, and the 3 year survival rate of the observation group was 41%, the control group was 16.4%, the observation group were significantly better than the control group (P<0.05). **Conclusion:** Bevacizumab combined with temozolomide could improve the quality of life, therapeutic efficacy and prolong the survival time of elderly postoperative patients with glioblastoma.

Key words: Bevacizumab; Temozolomide; Glioblastoma; Toxicity; Prognosis

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前言

胶质母细胞瘤是最常见的恶性原发性颅内肿瘤，也是高度血管化肿瘤，其特征为血管内皮生长因子(VEGF)的过表达。由于病变位置特殊，胶质母细胞瘤采用手术难以彻底切除，术后容易复发，为此需要在术后采用辅助治疗[1,2]。当前，术后替莫唑

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胺的应用使得患者预后得到一定改善,但仍不容乐观,中位生存期一般不超过 15 个月[3,4]。现代研究表明干扰 VEGF 的功能能够有效抑制胶质瘤的生长 [5,6]。贝伐单抗是种重组人单克隆 IgG 抗体,经美国食品和药物管理局(FDA)批准可用于治疗恶性肿瘤的一线用药[7]。贝伐单抗可破坏肿瘤组织内的新生血管,使已生成的肿瘤血管内皮细胞增殖,降低因肿瘤血管快速增殖导致的肿瘤侵袭,降低血管的通透性,增加血管内皮细胞密度,抑制肿瘤细胞向血管周围组织侵袭能力[8,9]。相关研究表明贝伐单抗联合替莫唑胺可使肿瘤对替莫唑胺的药物治疗敏感性增加,即增加替莫唑胺抗肿瘤作用[10],但在胶质瘤中的应用还无明确报道。本研究探讨了贝伐单抗联合替莫唑胺对老年胶质母细胞瘤术后患者预后的影响,现报道如下。

1 资料与方法

1.1 研究对象

选择 2014 年 1 月到 2016 年 1 月在第四军医大学西京医院诊治的老年胶质母细胞瘤术后患者 78 例,纳入标准:病理确诊为胶质母细胞瘤,并顺利完成手术;临床有可测量或可评估的病灶;年龄≥ 60 岁;肝肾功能和血常规正常;研究得到医院伦理委员会的批准;患者知情同意本研究。排除标准:合并心、肺、骨髓功能损害;既往有脑栓塞和脑出血病史。根据治疗方法的不同分为观察组与对照组各 39 例,两组的性别、年龄、体重指数、病灶部位、病理分期等对比无明显差异,具有可比性。

1.2 治疗方法

对照组:给予替莫唑胺 150-200 mg/m^2,空腹口服,d1-d5,28 d 为 1 个周期,连续治疗观察 2 个周期。

观察组:在对照组治疗的基础上给予贝伐单抗静脉输注治疗,剂量为 10 mg/kg,每 2 周给药 1 次为 1 个周期,连续给药 4 个周期。

1.3 观察指标

(1)疗效标准:采用神经肿瘤反应评估标准进行评定,完全缓解:临床情况稳定或有所改善,所有病灶完全消失并持续至少 3 个月,无新发病灶。部分缓解:临床情况稳定或改善,所有病灶最长径与垂直最宽径乘积之和)缩小 50%或以上,至少持续 3 个月。疾病稳定:不符合完全缓解、部分缓解标准。疾病进展:病灶至少增大 25%,出现新发病灶,临床情况恶化。完全缓解 + 部分缓解 = 有效。(2)毒副反应:按美国国立癌症研究所(NCI)3.0 标准进行评定,主要为肝肾反应、胃肠道反应、疲乏、骨髓抑制等。(3)KPS 与 ECOG 评分:所有患者在治疗前后进行 KPS 与 ECOG 评分,KPS 评分越高, 疾病状况越好;ECOG 评分越高,疾病状况越差。(4)生存情况:所有患者随访至今,记录患者的中位生存时间与 3 年生存率。

1.4 统计学分析

采用 SPSS 11.0 软件包进行统计学处理, 计量资料以均数± 标准差表示,采用配对 t 检验或者样本 t 检验,计数数据以百分率表示,采用 x^2 检验,采用 Kaplan-Meier 计算总生存率,对比采用 Log-rank 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床疗效对比

观察组与对照组的有效率分别为 48.7%和 23.1%, 观察组显著高于对照组(P<0.05)。见表 1。

表 1 两组临床疗效对比(n)

Table 1 Comparison of the curative effect between two groups (n)

Groups	n	Complete remission	Partial remission	Disease stabilization	Disease progression	Effective
Observation group	39	7	12	11	9	48.7%
Control group	39	4	5	18	12	23.1%
x^2						4.291
P						<0.05

2.2 两组毒副反应发生情况对比

观察组治疗期间的肝肾反应、胃肠道反应、疲乏、骨髓抑制等毒副反应的发生率明显低于对照组(P<0.05)。见表 2。

表 2 两组治疗期间毒副反应发生情况对比【例(%)】

Table 2 Comparison of the incidence of toxicity and side effects between two groups during treatment[n(%)]

Groups	n	Hepatic and renal response	Gastrointestinal reaction	Tired	Bone marrow transplantation
Observation group	39	5(12.8%)	7(17.9%)	6(15.4%)	6(15.4%)
Control group	39	12(30.8%)	18(46.2%)	17(43.6%)	14(35.9%)
x^2		3.331	4.278	6.471	4.182
P		<0.05	<0.05	<0.05	<0.05

2.3 两组治疗前后 KPS 与 ECOG 评分对比

观察组治疗后的 KPS 与 ECOG 评分分别为 64.22± 2.19 分和 1.65± 0.45 分,对照组为 56.35± 4.50 分和 2.41± 0.51 分,组间对比差异明显 (P<0.05), 且与治疗前对比也有明显差异(P<0.05)。见表 3。

2.4 两组术后生存情况对比

观察组与对照组的的中位生存时间分别为 30 个月和 21 个月, 观察组的 3 年生存率为 41.0%(16/39), 对照组为 16.4%(6/39),观察组都明显优于对照组(P<0.05)。

表 3 两组治疗前后 KPS 与 ECOG 评分对比(分,$\bar{x}\pm s$)

Table 3 Comparison of the KPS and ECOG score between two groups before and after treatment (points, $\bar{x}\pm s$)

Groups	n	KPS		t	P	ECOG		t	P
		Before treatment	After treatment			Before treatment	After treatment		
Observation group	39	30.55± 6.39	64.22± 2.19	13.298	<0.05	3.78± 0.73	1.65± 0.45	7.114	<0.05
Control group	39	30.11± 5.91	56.35± 4.50	8.224	<0.05	3.81± 0.87	2.41± 0.51	4.092	<0.05
t		0.223	5.398			0.045	3.298		
P		>0.05	<0.05			>0.05	<0.05		

3 讨论

胶质母细胞瘤是一种恶性胶质瘤，起源于神经胶质细胞，常呈浸润性生长、病死率高，且术后容易复发，预后更差，为此对于术后治疗的要求更高[11,12]。替莫唑胺作为一种新型抗肿瘤药物，是胶质瘤化疗的较好选择之一，其可作用于细胞分裂的各个时期，具有易通过血脑屏障、口服方便、耐受性好等特点[13]。但单独使用替莫唑胺既无法改善胶质母细胞瘤患者的缓解率，也无法延长其进展时间[14]。胶质母细胞瘤是富含血管的肿瘤，抑制肿瘤区新生血管内皮细胞生成、阻断血供已成为肿瘤治疗的一个重要策略[15]。研究表明 VEGF 在胶质瘤及肿瘤周围组织中均有表达，肿瘤的恶性程度越高，组织中 VEGF 的表达也增高[16]。贝伐单伐作为一种重组人源化单克隆抗体，可以特异性地与 VEGF 结合，抑制其生物学活性，进而达到抑制肿瘤生长的目的[17]。本研究结果显示观察组与对照组的有效率分别为 48.7%和 23.1%，KPS 与 ECOG 评分分别为 64.22± 2.19 分和 56.35± 4.50 分，1.65± 0.45 分和 2.41± 0.51 分，说明贝伐单抗联合替莫唑胺的应用能改善患者的生存质量，提高治疗疗效。

有效的抑制肿瘤血管异常生成可阻断肿瘤快速生长，起到杀灭肿瘤细胞的作用[18]。尽管贝伐单抗对患者改善患者的预后有重要作用，但是相关研究表明其也有一定的副反应[19,20]。本研究显示观察组治疗期间的肝肾反应、胃肠道反应、疲乏、骨髓抑制等毒副反应情况明显少于对照组，表明两者的联合用药能减少毒副反应的发生。原因主要在于贝伐单抗的使用安全，作用靶点确切，但也需要对贝伐单抗治疗的病例要制定个体化治疗，尽量避免毒副反应的发生[21]。此外，本研究显示观察组与对照组的的中位生存时间分别为 30 个月和 21 个月，3 年生存率分别为 41.0%、16.4%，也表明贝伐单抗与替莫唑胺联合使用可以延长胶质母细胞瘤术后患者的生存时间。

总之，贝伐单抗联合替莫唑胺在老年胶质母细胞瘤术后的应用能改善患者的生存质量，提高治疗疗效与延长患者的生存时间，且安全性较高。

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