专题报道

阿帕替尼单药方案治疗210例进展期胃癌的疗效及预后影响因素分析

郑华理,张　煌,周帅跃,朱爱萍
(安庆市第一人民医院,安徽 安庆 246000)

摘　要:[目的]探讨阿帕替尼单药方案治疗进展期胃癌的疗效及预后影响因素。[方法]回顾性分析210例接受阿帕替尼单药治疗的晚期胃癌患者临床资料,总结近期疗效、生存时间及安全性指标,评价阿帕替尼单药治疗晚期胃癌的预后影响因素。[结果]210例患者治疗后客观缓解率和疾病控制率分别为5.71%和65.71%;中位无进展生存时间为73.0 d;≥3级不良反应包括:高血压6例,合并手足综合征10例,蛋白尿4例,腹泻4例,血小板减少7例,疲倦2例,出血4例。单因素分析显示,PS评分、给药剂量、合并手足综合征、高血压、蛋白尿、腹泻及AFP水平与阿帕替尼单药治疗晚期胃癌疾病控制率有关(P<0.05);多因素分析显示,PS评分、合并手足综合征、高血压及AFP水平是阿帕替尼单药治疗晚期胃癌疾病控制率独立影响因素(P<0.05)。单因素分析显示,年龄、PS评分、给药剂量、合并手足综合征、高血压、蛋白尿及AFP水平与阿帕替尼单药治疗晚期胃癌无进展生存时间有关(P<0.05);多因素分析结果显示,PS评分、给药剂量、合并手足综合征、高血压及AFP水平是阿帕替尼单药治疗晚期胃癌无进展生存时间的独立影响因素(P<0.05)。[结论]阿帕替尼单药治疗晚期胃癌疾病控制效果与PS评分、合并手足综合征、高血压及AFP水平密切相关;PS评分、给药剂量、合并手足综合征、高血压及AFP水平能够独立影响患者无进展生存时间。

主题词:阿帕替尼;胃癌;疗效;预后;影响因素
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Efficacy and Prognostic Factors of Apatinib Monotherapy in the Treatment for 210 Cases with Advanced Gastric Cancer

ZHENG Hua-li, ZHANG Huang, ZHOU Shuai-yue, ZHU Ai-ping
(*The First People's Hospital of Anqing City*, *Anqing* 246000, *China*)

Abstract: [Objective] To investigate the efficacy and the prognostic factors of apatinib monotherapy in the treatment for advanced gastric cancer. [Methods] Clinical data of 210 stage Ⅳ gastric cancer treated with apatinib monotherapy were retrospectively analyzed. The clinical efficacy, survival time and safety indexes were analyzed and the prognostic factors of apatinib monotherapy for stage Ⅳ gastric cancer were evaluated. [Results] The objective response rate and disease control rate of 210 patients after treatment were 5.71% and 65.71%, respectively; the median progression free survival time was 73.0 d. Grade 3 adverse reactions included hypertension(n=6), combined hand-foot syndrome(n=10), proteinuria(n=4), diarrhea(n=4), thrombocytopenia(n=7), fatigue(n=2) and bleeding(n=4). Univariate analysis showed that PS score, dosage, combined hand-foot syndrome, hypertension, proteinuria, diarrhea and AFP levels were associated with the disease control rate of stage Ⅳ gastric cancer treated with apatinib monotherapy (P<0.05). Multivariate analysis showed that PS score, combined hand-foot syndrome and hypertension and AFP levels were independent influencing factors for disease control rate of stage Ⅳ gastric cancer treated with apatinib monotherapy (P<0.05). Univariate analysis showed that age, PS score, dosage, hypertension, combined hand-foot syndrome, proteinuria and AFP levels were associated with progression free survival in patients with stage Ⅳ gastric cancer (P<0.05). Multivariate analysis showed that PS score, dosage, combined hand-foot syndrome, hypertension and AFP levels were independent factors of progression free survival in patients with stage Ⅳ gastric cancer (P<0.05). [Conclusion] The disease control effect of apatinib monotherapy in patients with stage Ⅳ gastric cancer is closely related to PS score, combined hand-foot syndrome, hypertension and AFP levels; PS score, dosage, combined hand-foot syndrome, hypertension and AFP levels can independently affect progression free survival time.

Subject words: apatinib; gastric cancer; efficacy; prognosis; influencing factors

世界范围内胃癌发病率居恶性肿瘤第5位,而胃癌相关死亡率更高居第3位[1]。尽管部分胃癌患者接受根治性手术和术后辅助化疗方案治疗,但复发风险仍居高不下,临床预后极差[2]。目前认为血管内皮生长因子(vascular endothelial growth factor,VEGF)/血管内皮生长因子受体(VEGR receptor,VEGFR)-2

通信作者:朱爱萍,E-mail:zhuaiping666@sina.com
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是介导血管生成相关信号通路关键指标，广泛参与胃癌发生发展过程[3]。阿帕替尼是一种高选择性的VEGFR-2小分子酪氨酸激酶抑制剂(tyrosine kinase inhibitor,TKI)，具有抑制内皮细胞迁移和降低肿瘤微血管密度的双重作用[4]。研究显示,阿帕替尼单药能够提高晚期难治性或转移性胃癌患者整体生存获益,但治疗过程中较易出现高血压、合并手足综合征等多种不良反应，同时早期治疗有效人群随治疗时间延长往往出现耐药[5]。本文回顾性分析210例接受阿帕替尼单药治疗的晚期胃癌患者临床资料,总结近期疗效、生存时间及安全性指标,旨在探讨阿帕替尼单药方案治疗进展期胃癌的疾病控制率及复发风险影响因素。

1 资料与方法

1.1 临床资料

回顾性分析安庆市第一人民医院2016年5月至2019年12月收治的210例接受阿帕替尼单药治疗晚期胃癌患者临床资料。纳入标准:①经内镜及手术病理组织学检查确诊胃癌,包含胃食管结合部癌;②TNM分期Ⅳ期;③年龄≥18岁;④存在1个及以上可测量病灶;⑤二线及以上化疗失败;⑥PS评分0~2分;⑦临床资料完整。排除标准:①既往接受过VEGFR-TKI治疗；②血压>140 mmHg/90 mmHg;③第二原发肿瘤;④骨髓储备异常;⑤肝肾功能异常;⑥凝血功能异常。研究设计符合《赫尔辛基宣言》标准,且患者及家属签署知情同意书。本研究经医院伦理委员会批准(AQYY-YXLL-16-01)。

1.2 治疗方案

入选患者均给予甲磺酸阿帕替尼单药口服,初始剂量250 mg/次,1次/d。如无不良反应或1~2级不良反应且对症处理后消失,则1~2周后增加剂量达500 mg/d或750 mg/d,每4周为1个周期,直至疾病进展或无法耐受严重不良反应。

1.3 观察指标

近期疗效评估采用RECIST V1.0标准[6],其中客观缓解=完全缓解+部分缓解；疾病控制=完全缓解+部分缓解+疾病稳定；不良反应评估参考WHO标准。采用电话、门诊复查及住院病例查询等方式完成随访；随访终点事件包括疾病进展、死亡或失访。从治疗结束后开始随访,随访截止时间为2020年10月,出院后前2年每3~6个月随访1次,之后每6~12个月随访1次。

1.4 统计学处理

采用SPSS 20.0软件处理数据。计数资料比较采用χ^2检验；多因素分析采用Logistic回归模型和Cox比例风险模型;生存分析采用Kaplan-Meier法。P<0.05为差异有统计学意义。

2 结 果

2.1 近期疗效和生存时间

210例患者中位治疗周期数为3.0(1.0~4.0)个周期;治疗后达完全缓解、部分缓解、疾病稳定及疾病进展患者分别为0例、12例、126例和72例，客观缓解率和疾病控制率分别为5.71%和65.71%。随访过程中进展或死亡192例,失访18例,中位无进展生存时间为73.0 d。

2.2 安全性评估

210例患者随访期间出现不良反应包括：蛋白尿86例,高血压80例,白细胞减少74例,中性粒细胞减少64例,出血56例,血小板减少50例,合并手足综合征50例,腹泻32例,呕吐18例。其中≥3级不良反应包括:高血压6例,合并手足综合征10例,蛋白尿4例,腹泻4例,血小板减少7例,疲倦2例,出血4例。

2.3 疾病控制率影响因素分析

单因素分析结果显示,PS评分、给药剂量、合并手足综合征、高血压、蛋白尿、腹泻及AFP水平与阿帕替尼单药治疗晚期胃癌疾病控制率有关(P<0.05)(Table 1)。

多因素分析结果显示,PS评分、合并手足综合征、高血压及AFP水平是阿帕替尼单药治疗晚期胃癌疾病控制率独立影响因素(P<0.05)(Table 2)。

2.4 无进展生存时间影响因素分析

单因素分析结果显示，年龄、PS评分、给药剂量、合并手足综合征、高血压、蛋白尿及AFP水平与阿帕替尼单药治疗晚期胃癌无进展生存时间有关(P<0.05)(Table 3)。

多因素分析结果显示,PS评分、给药剂量、合并手足综合征、高血压及AFP水平均是阿帕替尼单药

Table 1 Univariate analysis of influencing factors of disease control rate of advanced gastric cancer treated with apatinib monotherapy

Index	Disease control (n=138)	Disease progression (n=72)	*P*
Gender			
Male	88	42	0.69
Female	50	30	
Age(years old)			
<55	54	40	0.15
⩾55	84	32	
PS score			
0~1	118	44	<0.01
2	20	28	
Number of metastases			
<3	106	60	0.48
⩾3	32	12	
Histopathological classification			
Papillary adenocarcinoma	6	0	0.48
Tubular adenocarcinoma	26	12	
Poorly differentiated adenocarcinoma	72	46	
Signet ring cell carcinoma	24	12	
Mucinous adenocarcinoma	10	2	
AFP			
Negative	122	60	0.53
Positive	16	12	
Tumor marker			
Normal	38	10	0.22
Elevation	100	62	
Previous treatment times			
2	114	50	0.17
⩾3	28	22	
Administration dose(mg)			
250	20	28	0.02
500	108	40	
750	10	4	
Hypertension			
Yes	66	14	<0.01
No	72	58	
Hand-foot syndrome			
Yes	48	2	<0.01
No	90	70	
Proteinuria			
Yes	68	18	0.02
No	70	54	
Bleeding			
Yes	94	60	0.11
No	44	12	
Diarrhea			
Yes	110	68	0.04
No	28	4	
Vomiting			
Yes	126	66	0.98
No	12	6	
Fatigue			
Yes	108	62	0.39
No	30	10	
Leukopenia			
Yes	84	52	0.87
No	54	20	
Neutropenia			
Yes	92	54	0.40
No	46	18	
Thrombocytopenia			
Yes	100	60	0.27
No	38	12	
AFP level(ng/mL)			
⩽20	131	53	<0.01
>20	7	19	

治疗晚期胃癌无进展生存时间独立影响因素（*P*<0.05）（Table 4）。

3 讨 论

阿帕替尼进入人体后可有效抑制 VEGF 与 VEGFR-2 间结合，拮抗 VEGFR-2 磷酸化，从而发挥抗肿瘤活性[7]。多中心Ⅲ期随机对照研究证实[8]，与安慰剂相比阿帕替尼治疗晚期胃癌中位无进展生存时间延长 0.8 个月，组间比较差异有统计学意义。本研究结果中，阿帕替尼组治疗 2 线及以上治疗失败晚期胃癌中位无进展生存时间为 73.0 d，与上述报道结果相符。

本研究结果证实 PS 评分是阿帕替尼单药治疗晚期胃癌疾病控制率和无进展生存时间独立影响因素。阿帕替尼主要通过抑制新生血管形成控制病情进展，但对于已生成的肿瘤血管并无显著退缩效应，故肿瘤负荷较大或机能状态较差患者往往疗效较差[9]。有报道显示老年恶性实体肿瘤患者微血管密度高于年轻患者，故对于抗血管靶向药物敏感性更佳[10]。本次研究单因素分析结果显示，年龄⩾55 岁患者无进展生存时间较<55 岁患者更长，与上述报道结果相符。

一项Ⅱ期临床试验针对胃癌患者分别给予阿帕替尼 850 mg/d 单次给药和两次给药方案治疗，客观缓解率分别为 6%和 13%，中位无进展生存时间分别为 3.8 个月和 3.3 个月[11]。本次研究在上述基础上降低剂量，结果显示阿帕替尼 500 mg/d 方案近期疗效和无进展生存获益更佳。目前尚无阿帕替尼针对 AFP 阳性晚期胃癌治疗报道，有研究证实 AFP 可与转录因子相互作用后刺激 VEGF-C 表达，推测其水平升高提示高侵袭性和预后不良[12]。考虑到 VEGFR-2 属于 VEGF-C 主要受体之一，故阿帕替尼也可通过抑制 VEGFR-2 调节 VEGF-C 作用，从而达到 AFP 阳性晚期胃癌预后的作用，但本次研究数据并未支持以上观点，有待后续更大规模研究进一步确证。

Table 2 Multivariate analysis of influencing factors of disease control rate in patients with advanced gastric cancer treated with apatinib monotherapy

Index	OR	95%CI	*P*
PS score	3.94	1.72~12.25	0.01
Hand-foot syndrome	0.07	0.03~0.44	0.01
Hypertension	0.53	0.17~0.85	0.04
AFP level	0.48	0.20~0.69	0.02

研究显示[13],抗血管生成药物治疗期间药物相关不良反应及程度与临床获益有关；其中阿帕替尼治疗后高血压出现可能与 NO 生物利用度下降有关,NO 可刺激血管收缩，降低肾脏钠离子排泄,诱发水钠潴留;而抗血管生成药物能够影响血管内皮功能,导致血管密度降低和血压升高。有报道显示存在 3 级及以上高血压胃肠道间质瘤患者给予抗血管生成药物治疗后无进展生存时间显著延长；同时阿帕替尼治疗实体肿瘤过程中出现高血压与无进展生存时间也独立相关[14]。本次研究结果中,出现高血压患者中位无进展时间和疾病控制率均优于未出现高血压患者,与上述报道结果相符。另有报道显示 VEGFR-TKI 治疗过程中随血压升高,患者中位无进展生存时间显著延长[15]。

手足综合征发病机制至今仍未完全阐明,大部分学者认为 VEGFR、PDGFR、RET 激酶及 FLT-3 信号传导通路与其发生发展有关。VGRFR-TKI 可通过抑制 VEGF 和 PDGF 活性,损伤毛细血管损伤,而手足等部位活动受压往往可造成伴随炎性反应手足综合征表现[16]。研究显示[17],既往 TKI 治疗失败患者接受其他类型 TKI 治疗时合并手足综合征严重程度往往降低；同时合并手足综合征患者生存获益增加,本次研究结果也证实这一观点。

已有研究显示，肾小球足细胞和内皮细胞均存在 VEGFR-2 表达,其磷酸化后能够通过调节肌动蛋白重组聚合,刺激足细胞形态改变,保护肾小球正常结构和功能[18]。阿帕替尼则可导致 VEGFR-2 磷酸化中断，影响内皮细胞增生，导致蛋白尿发生;同时蛋白尿还可为治疗有效潜在预测指标[19]。本研究单因素分析显示，合并蛋白尿患者疾病控制率和无进展生存时间均优于未合并者，但多因素分析结果未证实蛋白尿与阿帕替尼单药治疗Ⅳ期胃癌患者临床预后间独立关系，故仍有待后续研究确证。

本研究结果中,AFP 水平与患者疾病控制效

Table 3 Univariate analysis of influencing factors of progression free survival time of patients with advanced gastric cancer treated with apatinib monotherapy

Index	mPFS(95%CI)(d)	*P*
Gender		
Male	87.0(75.0~102.0)	0.19
Female	71.0(55.0~83.0)	
Age(years old)		
<55	54.0(44.0~65.0)	0.04
⩾55	92.0(77.0~109.0)	
PS score		
0~1	94.0(75.0~112.0)	<0.01
2	38.0(31.0~46.0)	
Number of metastases		
<3	75.0(60.0~92.0)	0.31
⩾3	73.0(58.0~89.0)	
Histopathological classification		
Papillary adenocarcinoma	190.0(153.0~241.0)	
Tubular adenocarcinoma	98.0(75.0~123.0)	
Poorly differentiated adenocarcinoma	71.0(55.0~87.0)	0.08
Signet ring cell carcinoma	65.0(51.0~80.0)	
Mucinous adenocarcinoma	62.0(47.0~74.0)	
AFP level(ng/mL)		
⩽20	72.0(56.0~87.0)	0.01
>20	98.0(76.0~130.0)	
Tumor marker		
Normal	97.0(83.0~121.0)	0.10
Elevation	65.0(50.0~79.0)	
Previous treatment times		
2	82.0(63.0~100.0)	0.92
⩾3	63.0(52.0~85.0)	
Administration dose(mg)		
250	44.0(35.0~54.0)	
500	90.0(74.0~112.0)	<0.01
750	93.0(77.0~114.0)	
Hypertension		
Yes	120.0(98.0~151.0)	<0.01
No	63.0(50.0~81.0)	
Hand-foot syndrome		
Yes	133.0(110.0~161.0)	<0.01
No	61.0(47.0~77.0)	
Proteinuria		
Yes	108.0(85.0~135.0)	<0.01
No	70.0(55.0~89.0)	
Bleeding		
Yes	65.0(51.0~80.0)	0.07
No	110.0(84.0~135.0)	
Diarrhea		
Yes	73.0(63.0~88.0)	0.11
No	106.0(83.0~133.0)	
Vomiting		
Yes	73.0(60.0~95.0)	0.74
No	72.0(58.0~91.0)	
Fatigue		
Yes	62.0(49.0~77.0)	0.19
No	84.0(66.0~105.0)	
Leukopenia		
Yes	71.0(60.0~89.0)	0.31
No	76.0(63.0~95.0)	
Neutropenia		
Yes	71.0(52.0~79.0)	0.45
No	73.0(55.0~81.0)	
Thrombocytopenia		
Yes	71.0(58.0~85.0)	0.68
No	75.0(60.0~90.0)	

Table 4 Multivariate analysis of influencing factors of progression free survival in patients with advanced gastric cancer treated with apatinib monotherapy

Index	OR	95%CI	*P*
PS score	2.05	1.23~3.40	0.01
Hand-foot syndrome	0.80	0.30~0.97	0.04
Hypertension	0.69	0.43~0.90	0.01
Administration dose(mg)			
250	1.00	–	0.01
500	0.53	0.34~0.85	0.46
750	0.82	0.48~1.97	<0.01
AFP level	0.71	0.55~0.89	0.02

果及无进展生存时间独立相关;既往报道认为血清AFP阳性(>20 ng/mL)者具有侵袭性强、早期易转移、疾病进展迅速等特点[20];AFP阳性胃癌患者同时性肝转移和异时性肝转移发生率分别达11.02%和32.24%,造成这一现象可能原因为此类患者体内*c-Met*基因高表达,可促进浆膜侵犯及远处转移[21]。

综上所述,阿帕替尼单药治疗晚期胃癌疾病控制效果与PS评分、合并手足综合征、高血压及AFP水平密切相关;PS评分、给药剂量、合并手足综合征、高血压及AFP水平能够独立影响患者无进展生存时间。考虑到阿帕替尼属于多靶点TKI抑制剂,故需进一步扩大样本量并于基因水平深入探索,从而真正实现胃癌的个体化治疗。

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