·临床研究·

# 阿帕替尼治疗老年晚期肝癌的临床效果及安全性

朱振华[1],褚行琦[2*]

([1]苏州市第九人民医院汾湖院区,苏州 215211;[2]上海交通大学医学院附属苏州九龙医院消化内科,苏州 215000)

**【摘 要】 目的** 探讨阿帕替尼治疗老年晚期肝癌的疗效及安全性。**方法** 收集2018年1月至2018年6月49例老年晚期肝癌患者,接受阿帕替尼单药治疗。按照RECIST1.1标准进行疗效评价,NCI-CTCAE version 4.0评价药物的不良反应并随访生存情况。应用Kaplan-Meier法进行生存分析,Cox回归模型进行多因素分析。**结果** 与治疗前相比,治疗4周后,患者病灶最大直径和及甲胎蛋白水平都降低,差异具有统计学意义($P<0.05$)。治疗12周后,患者客观缓解率(CR+PR)和疾病控制率(CR+PR+SD)分别为8.16%(4/49)和77.55%(38/49)。49例老年患者的中位无进展生存期(mPFS)为7.75个月。Cox多因素分析结果表明病灶最大直径和为独立影响因素[$HR$:1.866,95%$CI$(2.470~16.916),$P=0.000$]。不良反应发生率为100%,以1~2级为主。**结论** 阿帕替尼治疗老年晚期肝癌有一定疗效,且不良反应可控,可作为多线治疗失败的老年晚期肝癌患者的一种有效的治疗选择。

**【关键词】** 老年人;阿帕替尼;晚期肝癌;临床疗效;安全性

**【中图分类号】** R735.7 **【文献标志码】** A **【DOI】** 10.11915/j.issn.1671-5403.2020.05.084

# Efficacy and safety of apatinib in treatment of elderly patients with advanced hepatocellular cancer

ZHU Zhen-Hua[1], ZHU Xing-Qi[2*]

([1]Department of Gastroenterology, Fenhu Hospital District of Ninth People's Hospital of Suzhou Municipality, Suzhou 215211; [2]Department of Gastroenterology, Suzhou Jiulong Hospital Affiliated to Medical College of Shanghai Jiaotong University, Suzhou 215000, China)

**【Abstract】 Objective** To observe the efficacy and safety of apatinib in the treatment of the elderly patients with advanced hepatocellular cancer (HCC). **Methods** From January 2018 to June 2018, a total of 49 elderly patients were retrieved for the study, who were treated with apatinib for advanced hepatocellular cancer. Clinical efficacy was evaluated by RECIST 1.1 and side effects by NCI-CTCAE 3.0. Progression-free survival (PFS) was also observed. Kaplan-Meier survival analysis and Cox multivariate regression analysis were performed. **Results** The sum of maximum diameters of the lesion and alpha-fetoprotein levels were significantly reduced at 4 weeks of treatment as compared with those before the treatment ($P<0.05$). At 12 weeks of the treatment, the objective response rate, complete remission (CR) and partial remission (PR), was 8.16% (4/49), and disease control rate [CR, PR, and stable disease (SD)] was 77.55% (38/49). The median PFS of 49 patients was 7.75 months ($P<0.05$). Cox multivariate analysis showed that the sum of maximum diameters was an independent influencing factor [$HR$: 1.866, 95%$CI$(2.470-16.916), $P=0.000$]. The incidence of adverse reactions was 100%, mainly of grade 1-2. **Conclusion** Apatinib is effective for advanced HCC among the elderly patients with controllable adverse reactions and may serve as an option for those who have failed with multi-line treatment.

**【Key words】** aged; apatinib; advanced hepatocellular cancer; clinical efficacy; safety

*Corresponding author: ZHU Xing-Qi, E-mail: zhuxingqi_1@163.com*

肝癌(hepatocellular carcinoma,HCC)是我国常见的恶性肿瘤之一,年发病人数超过46万人,死亡人数超过42万,死亡率位居第3位[1]。肝癌起病隐匿,超过80%的患者发现时已属中晚期,已经失去了手术机会。对于晚期肝癌患者,放疗和化疗是目前主要的治疗手段。阿帕替尼是我国自主研制的小分子抗血管生成靶向药,可阻断肿瘤组织中血管内皮生长因子受体-2介导的微血管生成,最终达到抑制

**收稿日期**:2019-07-27;**接受日期**:2019-09-25

**通信作者**:褚行琦,E-mail:zhuxingqi_1@163.com

肿瘤生长的目的[2]。研究表明,阿帕替尼的药效作用随患者年龄变化而变化,其不良反应发生率在老年组中显著增高[3,4]。本研究旨在探讨阿帕替尼治疗老年晚期肝癌的疗效,并观察其安全性。

## 1 对象与方法

### 1.1 研究对象

收集2018年1月至6月来我院就诊、经病理组织学或细胞学检查确诊的老年晚期HCC患者,共49例。纳入标准:(1)年龄≥60岁;(2)Child-Pugh肝功能评级为A级或B级;(3)既往化疗失败或者复发转移;(4)预计生存期≥3个月。排除标准:(1)年龄≥80岁;(2)预计生存期<3个月;(3)严重冠心病、心律失常及心力衰竭等心脏疾病患者;(4)控制不良的高血压患者;(5)不愿参与本研究患者。本研究经我院伦理委员会批准,所有患者均签署知情同意书。

### 1.2 治疗方法

治疗方案:阿帕替尼250 mg/d,2次/d口服(阿帕替尼,商品名艾坦,购自江苏恒瑞医药股份有限公司,规格:0.25 g×10片×1板),每4周为1个治疗周期,若患者出现疾病进展或发生不可耐受的不良反应即停止用药。

### 1.3 观察指标

肝内病灶最大直径和:指肝内1个或2个最大的可测量病灶的最大直径和,超过2个病灶者只测量2个。应用Roche电化学发光法测定治疗前后血清甲胎蛋白(alpha-fetoprotein,AFP)水平。

### 1.4 疗效评价

参照《实体肿瘤的疗效评价标准RECIST指南1.1》版进行疗效评估,服药12周进行疗效评估,分为完全缓解(complete remission,CR)、部分缓解(partial remission,PR)、疾病稳定(stable disease,SD)、疾病进展(progressive disease,PD)。客观缓解率(objective remission rate,ORR)=(CR+PR)/总例数×100%;疾病控制率(disease control rate,DCR)=(CR+PR+SD)/总例数×100%。无进展生存期(progress free survival,PFS)指自服用阿帕替尼开始直至发生肿瘤进展或死亡的时间。

### 1.5 不良反应评价

按照NCI-CTCAE version4.0评分标准进行不良反应评价,将不良反应分为1~5级。

### 1.6 随访

采用电话随访和门诊复查对所有患者进行随访,每个月随访1次,随访终点为肿瘤进展或死亡。随访时间为2018年2月至2019年2月,无失访病例,中位随访时间为8个月。

### 1.7 统计学处理

采用GraphPad Prism 5.0软件对数据进行分析,以均数±标准差表示计量资料,以例数(百分率)表示计数资料,治疗前后比较采用配对$t$检验;生存分析采用Kaplan-Meier法,Cox比例风险模型进行多因素生存分析。$P<0.05$为差异具有统计学意义。

## 2 结 果

### 2.1 老年晚期肝癌患者临床资料分析

本研究共纳入49例老年晚期HCC患者,年龄61~79岁,中位年龄67岁,具体临床资料见表1。

**表1 老年晚期肝细胞癌患者的临床资料**

Table 1 Clinical data of elderly patients with advanced HCC

[$n$(%)]

| Item | Patients |
|---|---|
| Gender | |
| Male | 28(57.14) |
| Female | 21(42.86) |
| Child-Pugh grading | |
| A | 34(69.39) |
| B | 15(30.61) |
| Operative treatment | |
| Yes | 33(67.35) |
| No | 16(32.65) |
| Number of lesions | |
| 1 | 24(48.98) |
| 2 | 15(30.61) |
| 3 | 8(16.33) |
| ≥4 | 2(4.08) |
| Metastasis area | |
| Live | 23(46.94) |
| Celiac lymph nodes | 20(40.82) |
| Adrenal gland | 4(8.16) |
| Lungs and mediastinum | 10(20.41) |
| Portal vein tumor thrombus | 2(4.08) |
| HBV infection | 43(87.76) |
| AFP >400 ng/ml | 39(79.59) |
| Lesion maximum diameter sum >10 cm | 25(51.02) |

HBV: hepatitis B virus; AFP: alpha-fetoprotein.

### 2.2 疗效观察

2.2.1 病灶最大直径和与AFP水平变化情况 治疗4周后,49例老年晚期肝癌患者病灶最大直径和和AFP水平与治疗前相比均降低,差异具有统计学意义($P<0.05$,表2)。

2.2.2 疾病控制情况 治疗12周后进行疗效评价,49例老年晚期肝癌患者ORR和DCR分别为8.16%(4/49)和77.55%(38/49),具体见表3。

**表 2 肝癌患者治疗前后病灶最大直径和与 AFP 水平变化情况**

Table 2 Changes in sum of lesion maximum diameter and AFP levels of liver cancer patients before and after treatment

($\bar{x}\pm s$)

| Indicator | Before treatment | After treatment | $t$ | $P$ value |
|---|---|---|---|---|
| Sum of lesion maximum diameter(cm) | 9.23±1.06 | 7.19±1.47 | 7.88 | <0.001 |
| AFP(ng/ml) | 698.36±55.36 | 426.74±36.45 | 28.69 | <0.001 |

AFP: alpha-fetoprotein.

**表 3 阿帕替尼治疗老年晚期肝细胞癌患者的疗效**

Table 3 Effect of apatinib in treatment of elderly patients with advanced HCC [$n$(%)]

| Short-term efficacy | Patients |
|---|---|
| CR | 0(0.00) |
| PR | 4(8.16) |
| SD | 34(69.39) |
| PD | 11(22.45) |
| CR + PR | 4(8.16) |
| CR + PR + SD | 38(77.55) |

HCC: hepatocellular carcinoma; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease

2.2.3 无进展生存时间 49 例老年晚期肝癌患者中位无进展生存期(medium PFS, mPFS)为 7.75 个月。无进展生存期曲线见图 1。

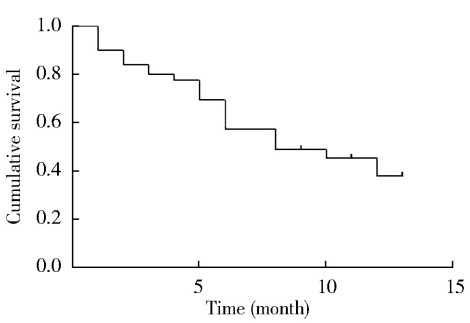



**图 1 阿帕替尼治疗老年晚期肝细胞癌患者的 PFS 生存曲线**

Figure 1 PFS curve of apatinib in treatment of elderly patients withadvanced hepatocellular carcinoma

PFS: progress free survival.

2.2.4 疾病进展影响因素分析 Cox 回归分析结果显示,病灶最大直径和为疾病进展的影响因素,见表 4。

### 2.3 安全性评价

49 例老年晚期肝癌患者均出现了不良反应,发生率为 100%。不良反应包括手足综合征、高血压、恶心呕吐、出血、肝损伤、骨髓抑制、乏力、腹泻、蛋白尿、口腔炎、声音嘶哑。大多数患者表现为 1~2 度不良反应,出现 3~4 度不良反应主要为高血压 4.08%(2/49)和手足综合征 4.08%(2/49),未出现 5 度不良反应。出现不良反应者,经短期停药或药物减量并给予对症处理后缓解。详见表 5。

**表 4 影响老年晚期肝细胞癌患者 PFS 的多因素 Cox 回归分析**

Table 4 Multivariate Cox regression analysis of PFS in elderly patients with advanced HCC

| Variable | Multivariate analysis $HR$(95%$CI$) | $P$ value |
|---|---|---|
| AFP | 0.851(0.585-9.375) | 0.230 |
| Diameter sum | 1.866(2.470-16.916) | 0.000 |
| Secondary hypertension | 0.517(0.688-4.090) | 0.255 |

PFS: progress free survival; HCC: hepatocellular carcinoma; AFP: alpha-fetoprotein.

**表 5 老年晚期肝癌患者的不良反应发生情况**

Table 5 Adverse reactions of elderly patients with advanced liver cancer ($n$=49)

| Adverse reaction | Level 1-2 | Level 3-4 | Total [$n$(%)] |
|---|---|---|---|
| Hand-foot syndrome | 23 | 2 | 25(51.02) |
| Hypertension | 22 | 2 | 24(48.98) |
| Nausea vomiting | 16 | 0 | 16(32.65) |
| Bleeding | 14 | 0 | 14(28.57) |
| Liver injury | 12 | 0 | 12(24.49) |
| Myelosuppression | 10 | 0 | 10(20.41) |
| Feeble | 10 | 0 | 10(20.41) |
| Diarrhea | 8 | 0 | 8(16.33) |
| Proteinuria | 7 | 0 | 7(14.28) |
| Stomatitis | 6 | 0 | 6(12.24) |
| Hoarseness | 2 | 0 | 2(4.08) |

## 3 讨 论

阿帕替尼是我国自主研制的抗血管生成药物,已被列入多种肿瘤三线治疗的基本药物。在多种肿瘤治疗中均有较好的疗效及生存获益[2,5,6]。文献报告[7],对 22 例晚期 HCC 患者采取每日口服 500 mg 阿帕替尼治疗,3 个月后,疾病稳定 16 例(72.73%),mPFS 为 7.2 个月。32 例无法切除或复发的晚期肝癌患者有效控制率为 60%,mPFS 和中位总生存期(medium overall survival,mOS)分别可达 5 个月和 13 个月[8],说明阿帕替尼对晚期 HCC 具有潜在生存获益。

由于老年人身体机能及脏器耐受性的降低,临床化疗的疗效在老年晚期肝癌患者成为一大难题。本研究通过回顾性分析 49 例老年晚期肝癌患者的临床资料显示,与治疗前相比,患者病灶最大直径和平均值及 AFP 平均水平都降低,客观缓解率和疾病控制率分别为 8.16%和 77.55%,mPFS 为 7.75 个月,

这与Zhen等[8]的研究结果接近。表明阿帕替尼单药对于老年晚期HCC患者具有一定的疾病控制和生存获益。Cox多因素分析结果显示,病灶最大直径和为影响疾病进展的独立影响因素。这与以前的研究结果一致,瘤体越小则预后越好[13,14]。

随着阿帕替尼在临床上的广泛应用,有关其不良反应的报道逐渐增多。本研究结果表明49例老年晚期肝癌患者不良反应发生率为100%。这个结果高于黄清云等[7]的研究结果(90.7%),推测可能与阿帕替尼所致不良反应以>50岁人群为主有关。本研究的结果还表明,大多数患者表现为1~2度不良反应,出现3~4度不良反应者,主要为高血压4.08%(2/49)和手足综合征4.08%(2/49),经短期停药或药物减量并给予对症处理后可缓解。提示阿帕替尼治疗老年晚期肝癌过程中出现的不良反应可控。

本文样本为来源于一所医院的49例HCC患者,属单样本观察性研究,结果具有一定的局限性。若要进一步证实阿帕替尼治疗老年晚期肝癌患者的疗效及安全性,还需随机对照试验结果的支持。

综上所述,阿帕替尼治疗老年晚期肝癌有一定疗效,且不良反应可控,可作为多线治疗失败的老年晚期肝癌患者的一种有效的治疗选择。

**【参考文献】**


[1] 陈世发, 赵礼金. 肝癌发生发展机制的研究进展及其治疗现状[J]. 中国普通外科杂志, 2018, 27(7): 910-923. DOI: 10.3978/j.issn.1005-6947.2018.07.016.
Chen SF, Zhao LJ. Research progress on mechanisms for occurrence of liver cancer and its treatment status[J]. Chin J Gen Surg, 2018, 27(7): 910-923. DOI: 10.3978/j.issn.1005-6947.2018.07.016.

[2] 胡猛, 刘星, 刘静, 等. 阿帕替尼治疗恶性肿瘤研究进展[J]. 中国老年学杂志, 2018, 38(19): 4858-4861. DOI: 10.3969/j.issn.1005-9202.2018.19.089.
Hu M, Liu X, Liu J, *et al*. Research progress of apatinib on malignant tumor[J]. Chin J Gerontol, 2018, 38(19): 4858-4861. DOI: 10.3969/j.issn.1005-9202.2018.19.089.

[3] Yu M, Gao Z, Dai X, *et al*. Population pharmacokinetic and covariate analysis of apatinib, an oral tyrosine kinase inhibitor, in healthy volunteers and patients with solid tumors[J]. Clin Pharmacokinet, 2017, 56(1): 65-76. DOI: 10.1007/s40262-016-0427-y.

[4] 时佳琪, 刘超, 张艳桥, 等. 甲磺酸阿帕替尼治疗恶性肿瘤的临床不良反应分析[J]. 中国肿瘤临床, 2018, 45(4): 191-195. DOI: 10.3969/j.issn.1000-8179.2018.04.269.
Shi JQ, Liu C, Zhang YQ, *et al*. Analysis of clinical adverse reactions of apatinib for the treatment of malignant tumors[J]. Chin J Clin Oncol, 2018, 45(4): 191-195. DOI: 10.3969/j.issn.1000-8179.2018.04.269.

[5] 顾小林, 陈大可, 顾建建, 等. 阿帕替尼治疗晚期非小细胞肺癌的临床疗效观察[J]. 临床合理用药杂志, 2019, 12(17): 43-44. DOI: 10.15887/j.cnki.13-1389/r.2019.17.025.
Gu XL, Chen DK, Gu JJ, *et al*. Efficacy of apatinib in patients with advanced non-small cell lung cancer[J]. Chin J Clin Rational Drug Use, 2019, 12(17): 43-44. DOI: 10.15887/j.cnki.13-1389/r.2019.17.025.

[6] 林岩松, 王宸, 李慧, 等. 甲磺酸阿帕替尼治疗进展性碘难治性甲状腺癌的短期疗效及安全性初步报告[J]. 中国癌症杂志, 2016, 26(9): 721-726. DOI: 10.19401/j.cnki.1007-3639.2016.09.001.
Lin YS, Wang C, Li H, *et al*. The preliminary report about the efficacy and safety evaluation of apatinib in progressive radioactive iodine-refractory differentiated thyroid cancer within 8 weeks[J]. China Oncol, 2016, 26(9): 721-726. DOI: 10.19401/j.cnki.1007-3639.2016.09.001.

[7] 黄清云, 王盼, 陈闯, 等. 阿帕替尼治疗22例晚期肝细胞癌的临床观察[J]. 重庆医学, 2019, 48(9): 1583-1586. DOI: 10.3969/j.issn.1671-8348.2019.09.035.
Huang QY, Wang P, Chen C, *et al*. Clinical observation on 22 cases with advanced hepatocellular carcinoma treated with apatinib[J]. Chongqing Med, 2019, 48(9): 1583-1586. DOI: 10.3969/j.issn.1671-8348.2019.09.035.

[8] Zhen L, Jiali C, Yong F, *et al*. The efficacy and safety of apatinib treatment for patients with unresectable or relapsed liver cancer: a retrospective study[J]. J Cancer, 2018, 9(16): 2773-2777. DOI: 10.7150/jca.26376. eCollection 2018.

[9] 沈雪敬, 张伟杰, 马志俊, 等. 阿帕替尼治疗晚期乳腺癌疗效与安全性分析[J]. 中华肿瘤防治杂志, 2019, 26(8): 549-553. DOI: 10.16073/j.cnki.cjcpt.2019.08.006.
Shen XJ, Zhang WJ, Ma ZJ, *et al*. Efficacy and safety of apatinib in patients with advanced breast cancer[J]. Chin J Cancer Prev Treat, 2019, 26(8): 549-553. DOI: 10.16073/j.cnki.cjcpt.2019.08.006.

[10] 胡月雷, 孙大伟, 骆飞翔, 等. 单发肝细胞癌发生微血管侵犯的影响因素及预后分析[J]. 临床肝胆病杂志, 2018, 34(09): 1911-1916. DOI: 10.3969/j.issn.1001-5256.2018.09.017.
Hu YL, Sun DW, Luo FX, *et al*. Influencing factors for microvascular invasion in patients with single hepatocellular carcinoma and their prognosis[J]. J Clin Hepatol, 2018, 34(9): 1911-1916. DOI: 10.3969/j.issn.1001-5256.2018.09.017.

[11] 张浩洋, 曹毅, 徐玥, 等. 乙肝相关性肝癌患者根治性切除术预后影响因素Cox回归分析[J]. 中国公共卫生, 2017, 33(11): 1646-1649. DOI: 10.11847/zgggws2017-33-11-27.
Zhang HY, Cao Y, Xu Y, *et al*. Influencing factors of prognosis among HBV-related HCC patients with radical resection: a Cox regression analysis[J]. Chin J Public Health, 2017, 33(11): 1646-1649. DOI: 10.11847/zgggws2017-33-11-27.

[12] 钱祥云, 戈伟. 阿帕替尼联合化疗治疗晚期胃癌临床分析[J]. 中华实用诊断与治疗杂志, 2017, 31(12): 1222-1224. DOI: 10.13507/j.issn.1674-3474.2017.12.023.
Qian XY, Ge W. Apatinib combined with chemotherapy for advanced gastric cancer[J]. J Chin Pract Diag Therapy, 2017, 31(12): 1222-1224. DOI: 10.13507/j.issn.1674-3474.2017.12.023.

[13] 赵青芳, 关露露, 吕慧芳, 等. 阿帕替尼治疗晚期胃癌的疗效预测和预后分析[J]. 中国癌症杂志, 2018, 28(03): 203-209. DOI: 10.19401/j.cnki.1007-3639.2018.03.006.
Zhao QF, Guan LL, Lv HF, *et al*. Analysis of the efficacy prediction and prognostic factors for advanced gastric cancer treated with apatinib[J]. China Oncol, 2018, 28(3): 203-209. DOI: 10.19401/j.cnki.1007-3639.2018.03.006.

[14] Itoh S, Yugawa K, Shimokawa M, *et al*. Prognostic significance of inflammatory biomarkers in hepatocellular carcinoma following hepatic resection[J]. BJS Open, 2019, 29, 3(4): 500-508. DOI: 10.1002/bjs5.50170.


(编辑: 门可)