doi: 10.3978/j.issn.2095-6959.2020.04.014
View this article at: http://dx.doi.org/10.3978/j.issn.2095-6959.2020.04.014

阿帕替尼在晚期胃癌姑息治疗中的临床观察

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[摘　要]　**目的：**评价阿帕替尼治疗方案，在二线化疗失败后晚期胃癌患者人群中的临床疗效及安全性。**方法：**选取空军军医大学唐都医院2015年9月至2018年8月收治的40例晚期胃癌二线化疗失败的患者，依照是否使用阿帕替尼药物治疗分为治疗组与对照组。治疗组使用阿帕替尼治疗；对照组则给予最优支持治疗。通过对比两组患者在治疗前后的近、远期疗效，不良反应发生率等临床指标，来评估阿帕替尼治疗方案在晚期胃癌患者中的客观疗效及安全性。**结果：**近期疗效观察中，治疗组客观缓解率(objective remission rate，ORR)、疾病控制率(disease control rate，DCR)优于对照组，DCR差异有统计学意义(80% vs 20%，P<0.05)。远期疗效指标上，治疗组中位总生存期overall survival，OS)6.1个月，中位无进展生存期(progression-free survival，PFS)3.0个月，对照组中位OS 3.7个月，中位PFS 1.8个月，治疗组亦优于对照组(P<0.05)。**结论：**阿帕替尼治疗方案对二线化疗失败后的晚期胃癌患者具有较为可靠的临床疗效及安全性。部分患者用药后疾病进程延缓，生活质量改善，生存期获得一定程度地延长，临床获益较为显著；同时药物不良反应轻微，大多数患者对药物的耐受情况良好。

[关键词]　阿帕替尼；晚期胃癌二线化疗失败；临床疗效；安全性

Clinical observation of apatinib in palliative treatment of advanced gastric cancer

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Abstract　**Objective:** To evaluate the clinical efficacy and safety of apatinib in patients with advanced gastric cancer after the failure of second-line chemotherapy. **Methods:** From September 2015 to August 2018, 40 patients with advanced gastric cancer who failed second-line chemotherapy were divided into a treatment group and a control group according to whether they were treated with apatinib or not. The treatment group was treated with apatinib, while the control group was treated with optimal support therapy. The objective efficacy and safety of apatinib in patients with advanced gastric cancer were evaluated by comparing the short-term and long-term efficacy and the incidence of adverse reactions between the 2 groups before and after the treatment. **Results:** In the short-term curative effect

收稿日期 (Date of reception)：2019–05–29
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基金项目 (Foundation item)：国家自然科学基金 (81502402)。This work was supported by the Natural Science Foundation of China (81502402).

observation, the objective remission rate (ORR), disease control rate (DCR) were better than those of the control group, and the differences of DCR were statistically significant (80% vs 20%, P<0.05). In the long-term curative effect index, the median overall survival (OS) of the treatment group was 6.1 months, the median PFS was 3.0 months, the median OS of the control group was 3.7 months, and the median PFS was 1.8 months. The OS and PFS in the treatment group was also superior to those of the control group (P<0.05). **Conclusion:** The apatinib treatment regimen after the failure of second-line chemotherapy in patients with advanced gastric cancer has a more reliable clinical efficacy and safety. Some patients delay the disease process, the quality of life has improved, the survival time is prolonged to a certain extent, and the clinical benefits are more significant. At the same time, the adverse drug reactions are mild, and most of the patients have good drug tolerance.

Keywords apatinib; failed second-line chemotherapy; advanced gastric cancer; clinical efficacy; safety

以往应用于胃癌的数种小分子靶向药物，如赫赛汀等，对于终末期Her-2阳性胃癌的治疗有效率不足20%，临床疗效难尽人意。可喜的是，近年研究证实，小分子抗血管生成靶向药阿帕替尼对于二线、三线化疗失败晚期胃癌的治疗效果较为突出[1-4]，而且正在逐渐拓展到治疗肺癌、妇科恶性肿瘤[5]、甲状腺癌[6]、肝癌、结直肠癌[7]等其他进展期恶性肿瘤[8-14]，因此，充分验证阿帕替尼在不同地区、人群、病种及治疗方案中的临床疗效和安全性十分必要。目前，关于阿帕替尼联合化疗方案的试验报道较多[15]，但单药姑息治疗晚期胃癌的相关疗效及安全性的可靠证据尚少。因此，本实验探索阿帕替尼单药治疗方案在不能耐受或拒绝放、化疗的转移性胃癌患者中的治疗效果及安全性。

1 对象与方法

1.1 对象

选取2015年9月至2018年8月空军军医大学唐都医院住院接受系统二线化疗，并评估为治疗失败的40例胃癌患者，其中男23例，女17例。患者均经组织病理活检确诊为胃癌。入选标准：年龄18~75岁；在接受过2种及以上系统化疗后，被评估为进展或复发的晚期胃腺癌患者；无消化道出血、慢性腹泻、肠梗阻、凝血功能异常、严重高血压、严重心脏疾病、严重肝肾功能障碍者；美国东部肿瘤协作组(Eastern Cooperative Oncology Group，ECOG)体力状况评分为0~2；靶病灶可通过影像学检查进行测量[满足实体瘤的疗效评价标准(Response Evaluation Criteria in Solid Tumors，RECIST) 1.1]，所有入选患者预计生存期应>3个月；所有患者既往未接受放疗，有症状的中枢系统转移患者除外。将以上入组病例随机分为治疗组和对照组，每组20例。两组一般资料差异没有统计学意义(P>0.05，表1)。

1.2 治疗方法

治疗组：口服阿帕替尼500 mg，1次/d，28 d为1个周期，直至观察到疾病进展或患者表示不能耐受药物毒副作用。对照组：最优支持治疗，包括营养支持、液体平衡、床旁护理、止痛抑吐等。两组均在治疗前测定基线，此后每月进行影像学检查，并在历次治疗周期结束后进行临床疗效及安全性评价，直至出现疾病进展或连续评价6个观察周期。

表1 两组一般资料比较

Table 1 Comparison of general data between the two groups

组别	性别 /[例 (%)]		年龄 /[例 (%)]		ECOG 评分 /[例 (%)]		既往化疗 /[例 (%)]		转移部位 /[例 (%)]	
	男	女	<60 岁	≥ 60 岁	0~1	2	三线	三线以上	一个脏器转移	多个脏器转移
阿帕替尼组	13 (65)	7 (35)	11 (55)	9 (45)	18 (90)	2 (10)	11 (55)	9 (45)	12 (60)	8 (40)
对照组	10 (50)	10 (50)	7 (35)	13(65)	17 (85)	3 (15)	6 (30)	13 (65)	11 (55)	9 (45)
P	0.532		0.341		1		0.2		1	

1.3 观察指标

近期疗效：通过随访患者病情，按RECIST标准，评估为完全缓解(complete response，CR)、部分缓解(partial response，PR)、稳定(stable disease，SD)和疾病进展(progress disease，PD)，同时计算客观有效率(objective remission rate，ORR)和疾病控制率(disease control rate，DCR)，观察期截止2018年8月31日。远期疗效：评估中位总生存期(overall survival，OS)及中位无进展生存期(progress free survival，PFS)，观察期截止随访结束。不良反应评价标准：采用国际肿瘤化疗药物不良反应评价标准(NCI CTCAE 4.0标准)进行评价。

1.4 统计学处理

使用SPSS 23.0软件进行数据分析。计数资料比较用χ^2检验。P<0.05为差异具有统计学意义。

2 结果

2.1 近期疗效

治疗组和对照组中均有部分患者表现为获益，两组间ORR差异没有统计学意义(20% vs 0%，P>0.05)，而两组间DCR差异则具有统计学意义(80% vs 20%，P<0.05，表2)。

2.2 远期疗效

截至随访结束，有1例患者存活，治疗组中位OS为6.1个月，中位PFS为3.0个月；对照组中位OS为3.7个月，中位PFS为1.8个月(图1，图2)。治疗组远期疗效较对照组更佳(P<0.05)。

表 2 两组近期疗效比较 (n=20)

Table 2 Curative effect after treatment between the 2 group (n=20)

组别	CR/[例 (%)]	PR/[例 (%)]	SD/[例 (%)]	PD/[例 (%)]	ORR/%	DCR/%
实验组	1 (5)	3 (15)	12 (60)	4 (20)	20	80
对照组	0 (0)	0 (0)	4 (20)	16 (80)	0	20
P					0.106	<0.05

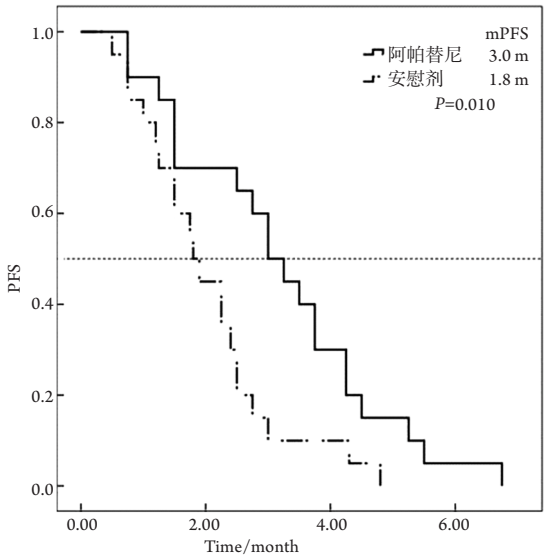

图1 组间PFS对比

Figure 1 Comparison of PFS between the 2 groups

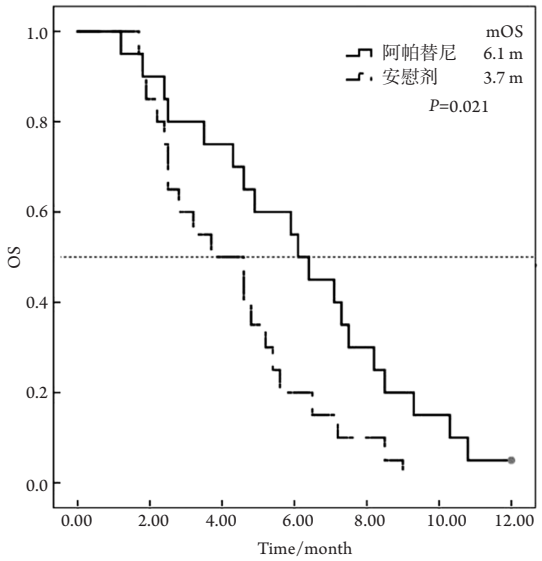

图2 组间OS对比

Figure 2 Comparison of OS between the 2 groups

2.3 不良反应

治疗组8例(40%)罹患高血压，9例(45%)表现出骨髓抑制，5例(25%)出现蛋白尿，3例(15%)罹患手足综合征。其中4例发生III~IV度严重不良反应(20%)。所有发生不良反应的患者，经过合理对症处理后，病情均可得到控制，总体耐受程度良好。

3 讨论

目前，我国临床上对晚期胃癌的治疗手段较为单一，以化疗为主的有限方案贯穿了晚期胃癌治疗的始终[16-17]。尽管部分一二线化疗药物疗效较为确切，但由于肿瘤不敏感、长期使用后耐药、个体基因差异等因素的存在，仍不可否认很大一部分胃癌患者在接受化疗后收效甚微[18-19]。更加不容乐观的是，由于一二线化疗方案毒副作用较为明显，不少晚期胃癌患者在接受治疗后，出现各种生理不适，生活质量反而下降，最后只能因难以耐受化疗而放弃延长生存时间的宝贵机会。因此积极探索更多安全有效的新型抗肿瘤药物势在必行。阿帕替尼作为我国自主研发的抗肿瘤药物，很有可能可以填补中晚期胃癌靶向治疗的这一空白。阿帕替尼是一种口服小分子血管内皮生长因子受体抑制剂，它通过高度选择性结合VEGF，继而竞争性抑制VEGFR-2配体，从而对肿瘤新生血管的生长起到抑制作用[20-22]。既往研究[23]表明：曲妥珠单抗联合阿帕替尼治疗可以改善胃癌患者生活质量。抗PD-1抗体SHR-1210联合阿帕替尼治疗晚期肝癌、胃癌或食管胃交界癌的毒性可控，ORR较高[24]。

本研究结果显示：阿帕替尼方案对二线化疗失败的晚期胃癌患者有一定的临床疗效，治疗组各疗效指标优于对照组，初步证明阿帕替尼在延缓晚期胃癌患者病情进展，延长生存期等方面具备较为可靠的疗效。值得一提的是，既往研究[25-28]表明：与传统化疗相比，阿帕替尼可靶向选择转导信号，因此常见不良反应较少，仅少数患者会出现出血压波动及肾功能下降。本研究也发现阿帕替尼治疗组中的部分患者，有血压升高、骨髓抑制、尿蛋白增高、手足综合征等不良反应的情况，这与既往研究[29]结论一致。

综上所述，二线化疗失败后的晚期胃癌患者选择阿帕替尼方案进行治疗，是一种较为安全可靠的临床决策。在提高肿瘤患者客观缓解率、疾病控制率，改善晚期胃癌患者生活质量各方面表现良好，值得在临床中进一步研究及推广。

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本文引用： 刘冬, 廖成功, 赵国宏, 兰飞, 赵鹏, 张贺龙. 阿帕替尼在晚期胃癌姑息治疗中的临床观察[J]. 临床与病理杂志, 2020, 40(4): 893-897. doi: 10.3978/j.issn.2095-6959.2020.04.014

Cite this article as: LIU Dong, LIAO Chenggong, ZHAO Guohong, LAN Fei, ZHAO Peng, ZHANG Helong. Clinical observation of apatinib in palliative treatment of advanced gastric cancer[J]. Journal of Clinical and Pathological Research, 2020, 40(4): 893-897. doi: 10.3978/j.issn.2095-6959.2020.04.014