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索拉非尼联合化疗栓塞治疗晚期原发性肝癌的疗效分析*

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摘要 目的:原发性肝癌(Primary hepatocellular carcinoma, PHC)是最常见的消化系统恶性肿瘤之一,严重威胁人类的健康。目前,治疗晚期肝癌的首选方法是肝动脉化疗栓塞(Transcatheter arterial chemoembolization, TACE),配合抗癌药物使用,治疗效果明显。索拉非尼因具有抑制肿瘤生长的作用而被越来越广泛的用于治疗肝癌。本研究针对索拉非尼的靶向性,探讨该药与化疗栓塞联合治疗晚期原发性肝癌的疗效,旨在为肝癌的临床治疗提供可参考的依据。**方法:**选取我院 2008 年 10 月-2012 年 6 月收治的晚期原发性肝癌患者 96 例,随机分为对照组和观察组,每组各 48 例。对照组患者采用肝动脉化疗栓塞单独治疗,观察组患者采用索拉非尼联合化疗栓塞治疗。比较两组患者的客观有效率、临床获益率、治疗一年生存率、两年以上生存率及甲胎蛋白(AFP)水平的变化情况。**结果:**观察组患者的客观有效率为 52.1%,临床获益率为 89.6%,均高于对照组患者的对应值 33.3%和 47.9%,差异有统计学意义($P<0.05$);观察组患者一年生存率为 89.6%,两年生存率为 72.9%,均高于对照组患者的对应值 58.3%和 35.4%,差异显著($P<0.05$);两组患者治疗后的 AFP 水平均比治疗前降低,观察组患者 AFP 水平的改善情况显著优于对照组,差异具有统计学意义($P<0.05$)。**结论:**索拉非尼联合化疗栓塞治疗晚期原发性肝癌具有明显的效果,且安全性高,值得临床推广使用。

关键词:索拉非尼;TACE;原发性肝癌;临床效果

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Clinical Effects of Sorafenib Combined with Transcatheter Arterial Chemoembolization on the Treatment of Advanced Primary Hepatocellular Carcinoma*

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ABSTRACT Objective: Primary hepatocellular carcinoma(PHC) is one of the most common malignant tumors in the digestion system which is a serious threat to human health. At present, the preferred method of the advanced PHC is the transcatheter arterial chemoembolization (TACE) that could be better when combined with the anti-cancer drugs. With the function of inhibiting tumor cells' growth, sorafenib has been widely applied on the treatment of liver cancer. In view of the targeted qualification of the sorafenib, this study is written to discuss the curative effects of sorafenib combined with TACE on the treatment of advanced primary liver cancer, so that we could provide some references for clinical research. **Methods:** 96 cases with the advanced hepatocellular carcinoma who were treated in our hospital from October 2008 to June 2012 were selected and randomly divided into the control group and the observation group with 48 patients in each group. The patients in the control group were treated only by the TACE, while the patients in the observation group were treated by the sorafenib combined with TACE. Then the objective response rate (ORR), the clinical benefit rate(CBR), the survival rate of one year, the survival rate of more than two years and the alphafetoprotein (AFP) changes of patients were compared between two groups. **Results:** The ORR of the patients in the observation group was 52.1% and the CBR was 89.6% which were higher than those of the patients in the control group(33.3% and 47.9%) with statistical significant differences($P<0.05$). The survival rate of one year and more than two years were 89.6% and 72.9% which were higher than those of the patients in the control group (58.3% and 35.4%) with statistical significant differences ($P<0.05$). The AFP levels were decreased of patients both in the two groups, but in which the observation group was superior to the control group ($P<0.05$). **Conclusion:** It's worthy to widely promote the application of sorafenib combined with TACE on the clinical field for the efficacy is obvious and safe for patients with the advanced hepatocellular carcinoma.

Key words: Sorafenib; TACE; Hepatocellular carcinoma; Clinical effects

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前言

原发性肝癌 (Primary hepatocellular carcinoma, PHC) 是消化系统的恶性肿瘤,每年全球约 65 万左右的新发肝癌病人,其中有一半以上发生在我国,不仅影响人类的身体健康,也给患者的家庭带来沉重的精神打击和经济负担^[1,2]。目前,临床上治疗中晚期肝癌的主要方式是肝动脉化疗栓塞 (Transcatheter arterial chemoembolization, TACE), 该方法通过导管将药物注入肝脏,使药物直接作用于肿瘤,最大限度地减少恶性肿瘤的数量和体积^[3-5]。肝癌在早期的临床症状不明显,得到确诊时往往已经错过治疗的最佳时机^[6]。那么,选择一种抑癌效果明显的靶向药物配合化疗栓塞治疗晚期肝癌是至关重要的。近年来,索拉非尼作为肝癌靶向治疗的首选药物具有双重抗肿瘤作用,既可通过阻断由 RAF/MEK/ERK 介导的细胞信号传导通路而直接抑制肿瘤细胞的增殖,还可通过作用于 VEGFR,抑制新生血管的形成,切断肿瘤细胞的营养来源,阻断细胞生长,从而延缓患者病情,延长生存时间,改善生存质量^[7-10]。本研究以晚期原发性肝癌患者为对象,旨在探讨索拉非尼联合 TACE 治疗晚期原发性肝癌的临床效果,为肝癌的治疗提供可借鉴的资料。现将研究结果报道如下:

1 资料与方法

1.1 临床资料

选取我院 2008 年 10 月 -2012 年 6 月收治的 96 例晚期原发性肝癌患者作为研究对象,经超肝动脉造影进行甲胎蛋白检查,根据原发性肝癌诊断标准及巴塞罗那分类标准^[11],所有患者均确诊为晚期原发性肝癌。将所选 96 例患者随机分为对照

组和观察组,每组 48 例。对照组男 31 例,女 17 例,年龄分布在 43-78 岁,平均年龄为(67.9± 10.8)岁;观察组男 34 例,女 14 例,年龄分布在 49-85 岁,平均年龄为(71.9± 12.7)岁。两组患者在性别、年龄、病程及病情等方面无明显差异,具有可比性。

1.2 方法

对照组采用 TACE 术行治疗。具体方法:患者局部麻醉,行股动脉穿刺,将 5F 导管置于肠系膜上动脉、肝总动脉、腹腔动脉、肝固有动脉造影,用超滑导丝将导管远端置于肿瘤供血动脉中,采用羟基喜树碱、阿霉素类、超液化碘油乳剂栓塞肿瘤血管^[12,13]。

观察组采用口服索拉非尼(400 mg/次,2 次/天)与 TACE 术(方法同对照组)联合治疗。

1.3 观察指标

观察两组患者治疗的客观有效率、临床获益率、1 年生存率、2 年以上生存率、AFP 水平的变化情况。

1.4 统计学方法

数据采用 spss17.0 进行分析处理,计量资料用 t 检验,定性资料比较用卡方检验,以 P<0.05 为差异具有统计学意义。

2 结果

2.1 两组患者治疗效果比较

对照组患者:完全缓解 0 例,部分缓解 16 例,病情稳定 7 例,病情持续进展 25 例,客观有效率为 33.3%,临床获益率为 47.9%;观察组患者:完全缓解 0 例,部分缓解 25 例,病情稳定 18 例,病情持续进展 5 例,客观有效率为 52.1%,临床获益率为 89.6%。观察组患者治疗的客观有效率和临床获益率均高于对照组,两组比较差异显著(P<0.05)。表 1。

表 1 两组患者的治疗效果比较

Table 1 Comparison of the clinical efficacy between two groups Group

Group	Case(n)	Remission	Partial remission	Stable	Continuos	ORR(%)	CR(%)
Control	48	0	16	7	25	33.3%	47.9%
Observation	48	0	25	18	5	52.1%	89.6%
P						<0.05	<0.05

2.2 两组患者治疗后的生存率比较

如表 2 所示,对照组患者一年生存率为 58.3%,两年以上生存率为 35.4%;观察组患者一年生存率为 89.6%,两年以上生存率为 72.9%。观察组患者治疗一年和治疗两年以上生存率均高于对照组,差异具有统计学意义(P<0.05)。

表 2 两组患者生存时间比较

Table 2 Comparison of the survival rate between two groups

Group	Case(n)	Survival rate(%)	
		One year	More than two years
Control	48	28(58.3)	17(35.4)
Observation	48	43(89.6)	35(72.9)
P		P<0.05	P<0.05

2.3 两组患者 AFP 水平比较

由表 3 可知,对照组患者治疗前 AFP 水平为(172.7± 14.3)

μg/L,治疗后为(134.8± 13.5)μg/L;观察组患者治疗前 AFP 水平为(176.9± 14.9)μg/L,治疗后为(83.9± 10.2) μg/L。两组患者治疗前 AFP 水平无显著差异 (P> 0.05); 两组患者治疗后的 AFP 水平与治疗前相比,均明显降低,且观察组患者 AFP 水平的改善情况优于对照组,差异具有统计学意义(P< 0.05)。

表 3 两组患者治疗前后的 AFP 水平比较(μg/L)

Table 3 Comparison of AFP levels of patients between two groups before and after treatment

Group	Case	AFP(Before treatment)	AFP(After treatment)
Control	48	172.7± 14.3	134.8± 13.5
Observation	48	176.9± 14.9	83.9± 10.2
P			P<0.05

3 讨论

原发性肝细胞癌在我国是一种常见的恶性肿瘤,起病隐

置,通常患者确诊时已属中晚期,失去了手术治疗的机会。研究表明,对于丧失手术切除机会的晚期原发性肝癌患者主要采用的是肝动脉化疗栓塞(TACE)术进行治疗,该技术自诞生三十年来,不断的完善和提高,目前已得到广泛的应用,其原理主要根据肝癌及肝脏的生理学特性进行治疗^[16]。据报道,TACE术能够在较高的肿瘤局部化疗药物浓度的作用下,最大限度的降低化疗药物的毒性对患者机体的损害,而且通过动脉栓塞减少对肿瘤的血供,使肿瘤细胞缺血缺氧而坏死凋亡^[17]。但由于肿瘤细胞具有耐药性、肿瘤新生血管复杂等因素,单纯使用TACE术不能完全杀死肿瘤细胞,必须联合靶向性药物治疗才能提高治疗效果。

索拉非尼是口服型多激酶抑制剂,可以抑制肿瘤细胞生长和肿瘤新生血管的形成。已有研究证实,索拉非尼能够平均延长晚期原发性肝癌患者的生存时间218个月,疾病进展时间217个月^[14,15]。相关研究表明,索拉非尼能够抑制丝氨酸-苏氨酸激酶和血管内皮生长因子受体22、血小板衍生生长因子受体-2, c2Kit, FLT3及Ret受体酪氨酸激酶,阻止肿瘤细胞增殖和新生血管的形成,进而抑制肿瘤生长。因此,索拉非尼联合TACE治疗晚期原发性肝癌可取得较好的疗效^[18-20]。结合本研究结果,观察组患者的客观有效率、临床获益率、1年生存率、2年以上生存率、AFP变化均优于对照组($P<0.05$)。这说明索拉非尼联合肝动脉化疗栓塞(TACE)用于治疗晚期原发性肝癌的临床效果优于单纯的介入手术治疗。

综上所述,索拉非尼联合肝动脉化疗栓塞(TACE)能够改善晚期原发性肝癌患者的疾病控制率,延长生存期,值得临床推广使用。

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