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FOLFOX 方案治疗胃癌的疗效及对血清 INF-γ 和 IL-4 水平的影响

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摘要 目的:探讨 FOLFOX 方案治疗胃癌的疗效及对血清干扰素 -γ(INF-γ)和白细胞介素 -4(IL-4)水平的影响。**方法:**选择我院 2011 年 1 月至 2014 年 1 月收治的胃癌患者 80 例,按随机数字表法平均分为两组,研究组及对照组各 40 例,以 3 周为 1 个疗程,治疗 3 个疗程。研究组患者给予 FOLFOX 方案治疗,对照组患者给予 ELF 化疗方案,3 个疗程后,比较两组患者治疗有效率,同时比较两组患者治疗前后血清 INF-γ 和 IL-4 水平变化及不良反应发生情况。**结果:**3 个疗程后,研究组患者治疗有效率为 57.5%,明显高于对照组 37.5%,比较差异具有统计学意义(P＜0.05)。两组患者治疗后血清 INF-γ 水平及 INF-γ/ IL-4 值较治疗前明显升高,而 IL-4 水平较治疗前明显下降,且研究组患者两种细胞因子水平改善程度均明显优于对照组,比较差异具有统计学意义(P＜0.05)。研究组患者白细胞减少、血小板下降及恶心呕吐不良反应发生率分别为 22.5%、7.5%及 27.5%,与对照组 25.0%、10.0%及 32.5%,比较差异无统计学意义(P＞0.05)。**结论:**FOLFOX 方案治疗胃癌效果显著,可有效改善患者机体免疫水平,提高抗肿瘤效果,值得临床推广应用。

关键词:胃癌;FOLFOX 方案;INF-γ;IL-4

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Efficacy of FOLFOX Regimen for Patients with Gastric Cancer and Its Effect on Levels of Serum INF-γ and IL-4

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ABSTRACT Objective: To investigate the curative effect of FOLFOX regimen in treatment of patients with gastric cancer and its effect on levels of serum interferon gamma (INF-γ) and interleukin -4(IL-4). **Methods:** A total of 80 patients with gastric cancer, admitted to the Affiliated Tumor Hospital of Xinjiang Medical University from January 2011 to January 2014, were randomly divided into study group(n=40) and control group(n=40). The study group was treated with FOLFOX regimen for 9 weeks(3 weeks was a course); while the control group was treated with ELF chemotherapy for 9 weeks. After 3 courses of treatment, the effective rates, levels of serum INF-γ and IL-4 before and after treatment, and incidence of adverse reactions of the two groups were compared. **Results:** After 3 courses of treatment, the effective rate (57.5%) of the study group was significantly higher than that (37.5%) of the control group, with significant difference (P<0.05). Compared with before therapy, serum INF-γ and INF-γ / IL-4 values of the two groups were significantly increased after treatment, but level of IL-4 decreased, and improvement of the two kinds of cytokines levels in the study group was significantly better than that of the control group, with significant difference (P<0.05). The adverse reaction rate of leukopenia, thrombocytopenia and nausea/vomiting of the study group was 22.5%, 7.5% and 27.5% respectively; of the control group, 25%,10.0% and 32.5% respectively. There was no significant difference between the two groups (P>0.05). **Conclusion:** FOLFOX regimen has a significant effect in the treatment of patients with gastric cancer,which can effectively improve the immune level of the body , enhance the anti-tumor effect and is worthy of clinical application.

Key words: Gastric cancer; FOLFOX regimen; INF-γ; IL-4

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前言

胃癌是临床常见的消化道恶性肿瘤，目前对于晚期胃癌，临床常用奥沙利铂、亚叶酸钙及氟尿嘧啶组成的 FOLFOX 化疗方案治疗[1-3]。有研究报道[4-6],胃癌的发生与发展患者的免疫功能具有显著相关性,干扰素 -γ(INF-γ)和白细胞介素 -4(IL-4)是免疫 Th1 及 Th2 细胞分泌的免疫应答因子，分别对细胞及体液免疫起到介导作用,因而在机体的免疫系统调节中发挥着及其中重要的作用。本研究对我院收治的 40 例胃癌患者使用 FOLFOX 方案治疗,疗效显著,现报告如下。

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1 资料与方法

1.1 一般资料

选择 2011 年 1 月至 2014 年 1 月我院收治的 80 例胃癌患者，均符合 WHO 胃癌诊断标准[7]，并经临床病理诊断确诊。其中男 45 例，男 35 例；年龄 29～70 岁，平均（45.9± 15.4）岁；TNM 分期：Ⅲ期 12 例，Ⅳ期 58 例；KPS 评分≥ 60 分；预计生存期＞3 个月；其中并发淋巴结转移 12 例，骨转移 6 例，肺转移 4 例。所有患者均为初次入院治疗，排除化疗明显禁忌症患者，按随机数字表法平均分为两组，研究组及对照组各 40 例，两组患者在性别、年龄、TNM 分期、并发症等方面比较差异无统计学意义（P＞0.05），具有可比性。

1.2 治疗方法

研究组患者使用 FOLFOX 方案化疗：第 1 d 奥沙利铂 130 mg / m^2+5%葡萄糖 500 mL，静脉滴注 3 h；第 2 d，亚叶酸钙（CF）300 mg+5%葡萄糖 250 mL 静脉滴注 2 h 后，静脉注射氟尿嘧啶（5-Fu）0.5 g，后接微泵（5 mL/h）持续静脉输注 4.5 g（54 h）。每 3 周重复一次，治疗 2 个周期。对照组患者采用 ELF 化疗方案：依托泊苷（VP-16）120 mg/m^2 第 1～3d；CF300 mg/m^2 第 1～3d；5-Fu500 mg/m^2 第 1～3 d，每 3 周为一个周期，治疗 2 个周期。

1.3 观察指标及疗效评价

疗效评价标准：依据 WHO 中胃癌疗效评价标准，分为完全缓解（CR）、部分缓解（PR）、稳定（SD）及恶化（PD）。有效率＝（CR+PR）/ 总例数× 100%。同时采用酶联免疫吸附法（ELISA）（美国 R&D 公司）测定患者血清 INF-γ 和 IL-4 水平，并记录患者治疗过程中不良反应发生情况，依据 WHO 推荐标准分为 0～Ⅳ度。

1.4 统计学处理

应用 SPSS17.0 分析数据，计量资料以平均数（$\bar{x}$± s）表示，进行 t 检验，计数资料采用 X^2 检验，以 P＜0.05 差异有统计学意义。

2 结果

2.1 两组患者治疗疗效比较

3 个疗程后，研究组患者治疗有效率为 57.5%，明显高于对照组 37.5%，比较差异具有统计学意义（X^2=5.24，P＜0.05）。

表 1 两组患者治疗疗效比较（n，%）

Table 1 Comparison of the curative effect of patients in two groups（n，%）

Groups	例数 n	CR	PR	SD	PD	总有效率 Total effective rate
研究组 Study group	40	7	16	12	5	57.5
对照组 Control group	40	3	12	16	9	37.5
X^2						5.24
P						＜0.05

2.2 两组患者治疗前后血清 INF-γ 和 IL-4 水平比较

两组患者治疗后血清 INF-γ 水平及 INF-γ/ IL-4 值较治疗前明显升高，而 IL-4 水平较治疗前明显下降，且研究组患者两种细胞因子水平改善程度均明显优于对照组，比较差异具有统计学意义（t=3.80，3.75，4.01，P＜0.05）。

表 2 两组患者治疗前后血清 INF-γ 和 IL-4 水平比较（$\bar{x}$± s）

Table 2 Comparison of the levels of serum INF-γ and IL-4 between patients in the two groups before and after treatment（$\bar{x}$± s）

组别 Groups	例数 n	时间 Time	INF-γ（ng/L）	IL-4（ng/L）	INF-γ/ IL-4
研究组 Study group	40	治疗前 Before treatment	704.3± 50.2	42.9± 5.3	13.9± 2.4
		治疗后 After treatment	1320.3± 94.3△▲	21.2± 1.5△▲	56.2± 3.3△▲
对照组 Control group	40	治疗前 Before treatment	712.3± 51.0	42.6± 5.8	13.5± 1.9
		治疗后 After treatment	1098.4± 95.0△	24.3± 1.2△	52.1± 5.9△

注：与治疗前比较，t=14.5,9.72,12.1,13.7,8.67,12.95，△P<0.05；与对照组同期比较，t=3.80,3.75,4.01，▲P<0.05。

Note:Compared with before treatment,t=14.5,9.72,12.1,13.7,8.67,12.95,△P<0.05;Compared with the control?group during the same period, t=3.80,3.75,4.01,▲P<0.05.

2.3 两组患者不良反应发生情况比较

研究组患者白细胞减少、血小板下降及恶心呕吐不良反应发生率分别为 22.5%、7.5%及 27.5%，与对照组 25.0%、10.0%及 32.5%，比较差异无统计学意义（X^2=0.43，0.24，0.50，P＞0.05）。

3 讨论

近年来，随着生活水平的提高以及环境污染的加剧，我国胃癌的发病率呈逐年上升趋势，患者死亡率位居各恶性肿瘤之

表 3 两组患者不良反应发生情况比较(n,%)

Table 3 Comparison of the occurrence of adverse reactions between patients in the two groups(n,%)

不良反应 Adverse reaction	组别 Groups	Ⅰ度 Ⅰ degree	Ⅱ度 Ⅱ degree	Ⅲ度 Ⅲ degree	Ⅳ度 Ⅳ degree	不良反应发生率 Adverse reaction rate
白细胞减少 Leukopenia	研究组 Study group	5	3	1	0	22.5
	对照组 Control group	6	2	2	0	25.0
血小板下降 Thrombocytopenia	研究组 Study group	2	1	0	0	7.5
	对照组 Control group	3	1	0	0	10.0
恶心呕吐 Nausea/vomiting	研究组 Study group	6	4	1	0	27.5
	对照组 Control group	7	4	2	0	32.5

首[8-10]。目前,临床最为有效的胃癌治疗手段为根治性切除术,术后患者 5 年生存率高达 30%[11],但多数患者发病至确诊时已处于晚期,失去了手术治疗的机会,因此化疗及放疗等辅助治疗成为晚期胃癌患者主要治疗手段。

有研究报道[12],胃癌对顺铂、蒽环类及紫杉醇类等化疗药物相对敏感,但经常规辅助化疗后效果一般。奥沙利铂是一类继顺铂及卡铂之后的第三代新型铂类抗癌药。临床研究表明[13-15],奥沙利铂可对大肠癌细胞株以及顺铂耐药细胞株等多种肿瘤细胞株起到显著抑制作用,与氟脲嘧啶联合应用可对耐药肿瘤起到有效治疗作用。FOLFOX 方案由奥沙利铂、亚叶酸钙及氟尿嘧啶组成,3 中抗癌药物联合应用可起到广谱体外细胞毒性以及体内抗肿瘤活性,同时消化道及骨髓抑制等不良反应较低。有研究报道[16],奥沙利铂与大剂量亚叶酸及 5-Fu 联合应用,作为二线治疗方案持续静脉滴注治疗转移性大肠癌,有效率为 42%,中位无进展生存期 6 个月。本研究对我院 40 例晚期胃癌患者,使用 FOLFOX 方案治疗,有效率为 57.5%,明显高于对照组的 37.5%,比较差异具有统计学意义(X^2=5.24,P<0.05)。结果进一步表明 FOLFOX 方案治疗晚期胃癌疗效显著。机体抗肿瘤免疫的效应机制包括细胞免疫和体液免疫。Th1 细胞及 Th2 细胞分别产生Ⅰ型细胞因子及Ⅱ型细胞因子,包括 IFN-1、IL-2、TNF-α 及 IL-4、IL-5、IL-6 等,分别起到介导细胞免疫及体液免疫应答的作用。在机体抗肿瘤作用主要通过 Thl 介导的细胞免疫效应,而一旦出现 Th1 类细胞因子向 Th2 类细胞因子漂移,则机体将处于免疫抑制状态,从而破坏抗肿瘤免疫作用。肿瘤黏膜中 INF-γ 表达水平降低可能是造成肿瘤细胞恶性增殖的重要因素。本研究中,两组患者化疗后外周血血清中 INF-γ 水平较化疗前明显升高,IL-4 水平明显降低,INF-γ/IL-4 明显增大,即 Th1 类细胞表达水平明显增强而 Th2 类细胞表达水平相对下降,提示,患者抗肿瘤作用明显增强。另外,研究组患者 INF-γ 及 IL-4 水平改善程度明显优于对照组,比较差异具有统计学意义(t=3.80,3.75,4.01,P<0.05),进一步表明 FOLFOX 方案化疗可有效调整机体的免疫状态,延缓疾病的发展,抗肿瘤效果显著。

总之,FOLFOX 方案治疗胃癌效果显著,可有效改善患者机体免疫水平,提高抗肿瘤效果,值得临床推广应用。

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