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西妥昔单抗联合化疗治疗 K-Ras 野生型转移性 结直肠癌的疗效及其影响因素分析 *

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摘要 目的:探讨西妥昔单抗联合化疗治疗 K-Ras 野生型转移性结直肠癌(mCRC)的疗效及其影响因素。**方法:**选取 2013 年 1 月~2015 年 1 月河北北方学院附属第一医院收治的 K-Ras 野生型 mCRC 患者 96 例,按照随机数字表法将患者分为对照组(n=48)和观察组(n=48)。对照组给予常规化疗方案治疗,观察组在此基础上给予西妥昔单抗治疗。比较两组临床疗效、中位无进展生存期(PFS)、中位总生存期(OS)以及不良反应发生情况,并分析观察组治疗疗效的影响因素。**结果:**观察组客观有效率(ORR)和疾病控制率(DCR)分别为 54.17%和 91.67%,均高于对照组的 31.25%和 81.25% ($P<0.05$)。观察组患者中位 PFS 和中位 OS 均较对照组长 ($P<0.05$)。观察组皮肤痤疮样病变发生率高于对照组 ($P<0.05$)。单因素分析显示,西妥昔单抗联合化疗治疗 K-Ras 野生型 mCRC 的 ORR、DCR 与年龄、肿瘤部位、肿瘤转移部位、肿瘤分化程度以及西妥昔单抗治疗时间有关 ($P<0.05$)。**结论:**西妥昔单抗联合化疗治疗 K-Ras 野生型 mCRC 疗效确切,预后较好,患者对不良反应可耐受,患者年龄、肿瘤部位、转移部位、分化程度及西妥昔单抗治疗时间可能是其疗效的影响因素。

关键词:西妥昔单抗; K-Ras 基因; 野生型; 转移; 结直肠癌; 化疗; 疗效; 影响因素

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Efficacy and Influencing Factors of Cetuximab Combined with Chemotherapy in the Treatment of K-Ras Wild-type Metastatic Colorectal Cancer*

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ABSTRACT Objective: To observe the efficacy and influencing factors of cetuximab combined with chemotherapy in the treatment of K-Ras wild-type metastatic colorectal cancer. **Methods:** 96 patients with K-Ras wild type mCRC who were admitted to First Affiliated Hospital of Hebei North University from January 2013 to January 2015 were selected. The patients were divided into control group (n=48) and observation group (n=48) according to the random number table method. The control group was treated with routine chemotherapy. The observation group was treated with cetuximab on this basis. The clinical efficacy, median progression-free survival (PFS), median overall survival (OS) and adverse reactions were compared between the two groups. The influencing factors of the efficacy of observation group were analyzed. **Results:** The objective response rate (ORR) and disease control rate (DCR) of the observation group were 54.17% and 91.67% respectively, which were higher than those of the control group 31.25% and 81.25% ($P<0.05$). The median PFS and OS in the observation group were longer than those in the control group ($P<0.05$). The incidence of acne-like lesions of skin in the observation group was higher than that in the control group ($P<0.05$). Univariate analysis showed that the ORR and DCR of cetuximab combined with chemotherapy for K-Ras wild type mCRC were related to age, tumor location, tumor metastasis site, degree of tumor differentiation and treatment time of cetuximab ($P<0.05$). **Conclusion:** Cetuximab combined with chemotherapy in the treatment of K-Ras wild type mCRC has definite efficacy and good prognosis. Patients can tolerate adverse reactions. The age, tumor location, metastasis site, differentiation degree and treatment time of cetuximab may be the influencing factors of its efficacy.

Key words: Cetuximab; K-Ras gene; Wild-type; Metastatic; Colorectal cancer; Chemotherapy; Efficacy; Influencing factor

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前言

结直肠癌(Colorectal cancer, CRC)是目前世界范围内第三大类肿瘤,病死率约占全部恶性肿瘤的第四位,且发病率呈逐年上升趋势^[1]。CRC早期症状不显著,多数患者确诊时已发展至中晚期,且患者常伴有肿瘤转移,并进展为转移性结直肠癌(Metastatic colorectal cancer, mCRC),因此mCRC在临床中更为多见^[2,3]。目前治疗mCRC的靶向药物有血管内皮细胞生长因子(Vascular endothelial growth factor, VEGF)抑制剂、表皮生长因子受体(Epidermal growth factor receptor, EGFR)抑制剂和环氧合酶-2(COX-2)抑制剂等^[4]。有研究发现,mCRC常常伴随基因突变,如K-Ras突变,且突变后的mCRC不再受EGFR调控,此时针对EGFR靶点进行治疗的药物将失效^[5,6],因此EGFR抑制剂仅适用于K-Ras野生型mCRC的治疗。西妥昔单抗属于免疫球蛋白G1(Immunoglobulin G1, IgG1)型单克隆抗体,其可通过与EGFR特异性结合,从而抑制肿瘤细胞增殖、分化,进而发挥抗肿瘤作用。有研究^[7]显示,一线化疗联合西妥昔单抗治疗恶性肿瘤可使患者获得更长生存期,但仅有40%-50%的患者可获益,具体哪些因素可以影响其疗效目前尚不清楚。鉴于此,本研究通过分析西妥昔单抗联合化疗治疗K-Ras野生型mCRC的疗效及疗效的影响因素,以期临床提供参考。

1 资料与方法

1.1 一般资料

选取2013年1月~2015年1月河北北方学院附属第一医院收治的K-Ras野生型mCRC患者96例,纳入标准:(1)所有患者均符合中国抗癌协会制定的《新编常见恶性肿瘤诊治规范》中CRC诊断标准^[8],并经CT或MRI或PET/CT及病理学确诊为mCRC;(2)通过突变扩增系统^[9](ARMS)检测,K-Ras基因第12、13、61位点密码子为野生型;(3)未接受放疗或其他抗肿瘤治疗者;(4)预计生存期 ≥ 6 个月;(5)Kamofsky(KPS)评分^[10] ≥ 60 分。排除标准:(1)对化疗和分子靶向治疗无法耐受者;(2)合并其他心、脑等严重疾病者;(3)妊娠期或哺乳期妇女;(4)有严重感染性疾病、肝肾功能障碍、药物禁忌症者;(5)精神疾病者。按照随机数字表法将患者分为对照组($n=48$)和观察组($n=48$)。对照组男性27例,女性21例;年龄35~70岁,平均年龄(58.68 ± 2.20)岁;平均KPS评分(65.37 ± 3.42)分;肿瘤部位:直肠及左半结肠32例,右半结肠16例;肿瘤转移部位:单器官转移17例,多器官转移31例;肿瘤分化程度:低分化15例,中分化23例,高分化10例。观察组男性25例,女性23例,年龄34~71岁,平均年龄(58.29 ± 3.10)岁;平均KPS评分(64.29 ± 3.50)分;肿瘤部位:直肠及左半结肠30例,右半结肠18例;肿瘤转移部位:单器官转移16例,多器官转移32例;肿瘤分化程度:低分化17例,中分化24例,高分化7例。两组患者一般资料比较无差异($P>0.05$),具有可比性。

1.2 治疗方法

对照组给予常规化疗,方案包括:(1)以伊立替康为基础的方案,如FOLFIRI[第1d伊立替康(上海创诺制药有限公司,国药准字:H20123191)180 mg/m² ivgtt;第1-2d亚叶酸钙(哈尔滨三联药业股份有限公司,国药准字:H20034072)200 mg/m²

ivgtt;第1-2d氟尿嘧啶(上海旭东海普药业有限公司,国药准字:H31020593)200 mg/m² ivgtt,600 mg/m²持续微量泵入48h,2周为1个周期];XELIRI[第1d伊立替康250 mg/m² ivgtt;第1-14d卡培他滨片(齐鲁制药有限公司,国药准字:H20133361)850-1250 mg/m² po bid,3周为1个周期];单药CPT-11(第1、8d伊立替康125 mg/m² ivgtt30-90 min,3周为1个周期)。(2)以奥沙利铂为基础的方案,如FOLFOX4[第1d奥沙利铂(南京制药厂有限公司,国药准字:H20000686)85 mg/m² ivgtt;第1-2d亚叶酸钙200 mg/m² ivgtt;第1-2d氟尿嘧啶400 mg/m² ivgtt,600 mg/m²持续微量泵入48h,2周为1个周期];XELOX(第1d奥沙利铂130 mg/m² ivgtt;第1-14d卡培他滨片850-1000 mg/m² po bid,3周为1个周期);(3)以单药卡培他滨化疗,第1-14d卡培他滨片1250 mg/m² po bid,3周为1个周期。观察组在对照组基础上给予西妥昔单抗(德国Merck KGaA,注册证号:S20130004)ivgtt,首次400 mg/m²,120min,其后每周1次,250 mg/m²,或每2周1次,500 mg/m²,2-3周为1个疗程,两组患者均治疗6个疗程。

1.3 疗效判定标准^[11]

完全缓解(Complete remission, CR):病理性淋巴结短径减少10 mm以上,靶病灶消失;部分缓解(Partial remission, PR):基线靶病灶直径之和减少30%以上;疾病稳定(Stable disease, SD):基线靶病灶直径之和减少20%~30%;疾病进展(Progression disease, PD):基线靶病灶直径之和减少小于20%或出现新病灶。根据以上标准计算客观有效率(Objective response rate, ORR)和疾病控制率(Disease control rate, DCR), $ORR = (CR + PR) / \text{总例数} \times 100\%$, $DCR = (CR + PR + SD) / \text{总例数} \times 100\%$ 。

1.4 生存期评价^[12]

生存期以中位无进展生存期(Progression-free survival, PFS)、中位总生存期(overall survival, OS)进行评价。PFS是指从患者接受西妥昔单抗治疗开始至出现疾病进展的时间,或至因任何原因死亡的时间。OS是指从患者接受西妥昔单抗治疗开始至患者死亡或观察截止的时间。

1.5 统计学分析

采用SPSS 17.0软件进行数据分析。计数资料以率表示,采用 χ^2 检验,计量资料以($\bar{x} \pm s$)表示,采用t检验,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 两组患者临床疗效比较

观察组ORR和DCR分别为54.17%和91.67%,高于对照组的31.25%和81.25%,差异具有统计学意义($P<0.05$)。见表1。

2.2 两组患者中位PFS和中位OS比较

观察组患者中位PFS和中位OS分别为(10.37 ± 1.89)个月和(20.18 ± 2.76)个月,均较对照组的(6.31 ± 1.76)个月和(15.03 ± 1.53)个月长,差异有统计学意义($t=4.971, 5.163, P=0.000, 0.000$)。

2.3 两组患者不良反应比较

两组均未见因不良反应而停药者。观察组皮肤痤疮样病变发生率高于对照组($P<0.05$),而两组白细胞下降、肝功能损伤、

恶心、呕吐及神经毒性发生率比较无差异($P>0.05$)。见表 2。

2.4 西妥昔单抗联合化疗治疗 K-Ras 野生型 mCRC 疗效的影响因素分析

单因素分析显示,西妥昔单抗联合化疗治疗 K-Ras 野生型

mCRC 的 ORR、DCR 与年龄、肿瘤部位、肿瘤转移部位、肿瘤分化程度以及西妥昔单抗治疗时间有关($P<0.05$),而与性别、联合化疗方案、早期肿瘤是否缓解无关($P>0.05$)。见表 3。

表 1 两组临床疗效比较 [例(%)]

Table 1 Comparison of clinical efficacy between the two groups [n (%)]

Groups	n	CR	PR	SD	PD	ORR	DCR
Observation group	48	6(12.50)	20(41.67)	18(37.5)	4(8.33)	26(54.17)	44(91.67)
Control group	48	4(8.33)	11(22.92)	24(50.00)	9(18.75)	15(31.25)	39(81.25)
χ^2						-2.266	-4.255
P						0.023	0.010

表 2 两组患者不良反应比较 [例(%)]

Table 2 Comparison of adverse reactions between the two groups [n (%)]

Groups	n	Leukocyte decline	Acne-like lesions of skin	Liver function damage	Nausea and vomiting	Neurotoxicity
Observation group	48	13(27.08)	23(47.92)	7(14.58)	12(25.00)	10(20.83)
Control group	48	10(20.83)	7(14.58)	9(18.75)	8(16.67)	7(14.58)
χ^2		0.515	12.412	0.300	1.011	0.643
P		0.473	0.000	0.584	0.315	0.423

表 3 西妥昔单抗联合化疗治疗 K-Ras 野生型 mCRC 疗效的影响因素分析

Table 3 Analysis of influencing factors of efficacy of cetuximab combined with chemotherapy in the treatment of K-Ras wild-type mCRC

Factors		n	ORR n(%)	χ^2	P	DCR n(%)	χ^2	P
Age(years)	≤ 65	32	18(56.25)	4.923	0.027	30(93.75)	11.636	0.001
	>65	16	8(50.00)			14(87.50)		
Gender	Male	25	14(56.00)	0.071	0.790	23(92.00)	0.182	0.670
	Female	23	12(52.17)			21(91.30)		
Tumor location	Rectum and left-sided colon	30	23(76.67)	16.313	0.000	29(96.67)	8.909	0.003
	Right-sided colon	18	3(16.67)			15(83.33)		
Tumor metastasis site	Single argan	16	12(75.00)	4.196	0.041	15(93.75)	11.636	0.001
	Multiple organ	32	14(43.75)			29(90.63)		
Degree of tumor differentiation	Poorly differentiated	17	8(47.05)	4.620	0.030	14(82.35)	3.966	0.046
	Moderately differentiated	24	13(54.17)			23(95.83)		
	High differentiated	7	5(71.43)			7(100.00)		
Combined with chemotherapy	Irinotecan-based	22	12(54.55)	0.027	0.870	21(95.45)	0.942	0.332
	Oxaliplatin-based	21	11(52.38)			20(95.24)		
	Capecitabine-singled	5	3(60.00)			3(60.00)		
Early tumor remission	Yes	27	15(55.56)	2.692	0.061	26(96.30)	2.909	0.088
	No	21	11(52.38)			18(85.71)		
Treatment time of cetuximab	<16 weeks	38	20(52.63)	15.077	0.000	34(89.47)	35.636	0.000
	≥ 16 weeks	10	6(60.00)			10(100.00)		

3 讨论

由于 K-Ras 基因片段内包含 4 个编码外显子和 1 个非编

码外显子,且其 2 号编码外显子具有高基因突变性,因此其在恶性肿瘤中极易发生突变,从而将导致 EGFR 正常的生物学作用受抑制,引起细胞病理性持续增殖,最终诱导细胞发生癌

变^[13-15]。在 mCRC 的发生过程中,常涉及 K-Ras 基因在内的多种基因参与调控,因此目前大部分观点认为对存在 K-Ras 突变型的 mCRC 患者,应用 EGFR 抑制剂常会导致治疗无效^[16,17],故 EGFR 抑制剂常只用于 K-Ras 野生型 mCRC 的治疗。西妥昔单抗是 2003 年批准上市的一种重组的嵌合 IgG1 单克隆抗体^[18],可竞争性地与肿瘤细胞表面的 EGFR 特异性结合,从而可以阻断细胞内 EGFR 介导的信号通路,进而可以抑制肿瘤细胞增殖、分化和转移^[19,20]。同时,西妥昔单抗中含有部分人源化成分,可作为外源性抗体杀灭肿瘤细胞^[21,22]。研究^[23]显示,与 FOLFOX/FOLFIRI 一线化疗方案比较,西妥昔单抗联合化疗可改善患者生存结局,延长生存时间,但又有研究^[24]显示,接受西妥昔单抗治疗的患者中仅有不到一半患者会受益,提示可能还存在其他影响其疗效的复杂因素。

本研究结果显示,观察组 ORR、DCR 明显高于对照组。ORR、DCR 可以体现 mCRC 实体肿瘤直径变化情况的,反映 mCRC 缓解的程度,因此以上结论提示西妥昔单抗联合化疗可提高疗效。本研究结果显示,观察组患者中位 PFS 和中位 OS 均较对照组延长($P<0.05$),提示西妥昔单抗联合化疗可以延长 K-Ras 野生型 mCRC 患者的生存时间。另外,本研究结果还显示,观察组皮肤痤疮样病变发生率高于对照组,而两组肝功能损伤、恶心、白细胞下降、呕吐及神经毒性发生率比较无差异,提示西妥昔单抗治疗 K-Ras 基因野生型 mCRC 不会明显增加胃肠道、神经毒性等不良反应,具有较好的安全性^[25-27]。本研究结果显示,患者年龄、肿瘤部位、肿瘤转移部位、分化程度、西妥昔单抗治疗时间与西妥昔单抗联合化疗治疗 K-Ras 野生型 mCRC 的 ORR、DCR 有关。随着年龄的增长,患者机体免疫力逐渐降低,且恶性肿瘤的侵袭将导致抗病能力下降,因此患者年龄一定程度上将影响西妥昔单抗的疗效^[28,29]。本研究结果显示,病发于直肠及左半结肠的患者 ORR、DCR 均显著高于右半结肠患者,提示不同发病部位亦是疗效的影响因素。分析原因,可能与不同部位对化疗方案或靶向治疗药物的敏感性不同有关^[30]。而对于肿瘤转移至多器官的患者,其器官受损程度更严重,范围也更广,增加了机体的负担,因此其治疗难度加大,疗效也将受影响。同时不同分化程度的 K-Ras 基因野生型 mCRC 的疗效也不尽相同。分析原因可能与分化程度不同,肿瘤侵袭性不同有关。CRC 属于慢性肿瘤疾病,临床中常常需长期服药,本研究中接受西妥昔单抗治疗时间较长的患者其 ORR、DCR 相对更高,分析原因可能与药物的持续作用可对肿瘤细胞产生抑制有关。

综上所述,西妥昔单抗联合化疗治疗 K-Ras 基因野生型 mCRC 疗效确切,可以提高患者生存期,患者对不良反应可耐受,患者年龄、肿瘤部位、肿瘤转移部位、分化程度及西妥昔单抗治疗时间可能是影响其疗效的因素。

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