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贝伐珠单抗联合化疗治疗晚期结直肠癌的临床疗效

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摘要 目的:探讨晚期结直肠癌采用贝伐珠单抗联合化疗的临床疗效,为临床治疗提供参考。**方法:**按照随机数字表法将2010年2月～2013年2月我院收治的50例晚期结直肠癌患者分为两组,观察组采用贝伐珠单抗联合奥沙利铂,卡培他滨化疗,对照组单用奥沙利铂,卡培他滨进行化疗,比较两组的临床疗效、血清肿瘤标志物浓度变化及不良反应。**结果:**化疗4个周期后观察组有效率为56.00%高于对照组的24.00%,差异有统计学意义(P<0.01),观察组疾病控制率为84.00%高于对照组的60.00%,差异有统计学意义(P<0.05);观察组治疗后的CEA、CA242、CA19-9浓度均低于对照组,差异有统计学意义(P<0.01);化疗后两组不良反应主要有恶心、呕吐、食欲减低等胃肠道反应,乏力,肝功能损害,骨髓抑制,脱发,贫血以及中性粒细胞下降等,其中观察组乏力,肝功能损害发生率低于对照组,差异有统计学意义(P<0.05),其余不良反应两组差异无统计学意义(P>0.05)。**结论:**结直肠癌采用贝伐珠单抗联合化疗治疗具有近期疗效好,安全性高等特点,临床有重要参考价值。

关键词:晚期结直肠癌;化疗;贝伐珠单抗

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Efficacy of Bevacizumab Combination with Chemotherapy in the Treatment of Advanced Colorectal Cancer

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ABSTRACT Objective: To explore the clinical efficacy of bevacizumab in combination with chemotherapy in the treatment of advanced colorectal cancer, and to provide reference for the clinical treatment. **Methods:** 50 cases of patients with advanced colorectal cancer in our hospital from February 2010 to February 2013 were divided into two groups according to the random number table method, the observation group were given bevacizumab combination with Oxaliplatin and Capecitabine, the control group was treated with Oxaliplatin,Capecitabine chemotherapy, the clinical effect, serum tumor marker concentration changes and adverse reactions of the two groups were compared. **Results:** After 4 cycles of chemotherapy, the effective rate of the observation group was 56.00%, higher than that of the control group (24.00%), and the difference was statistically significant (P<0.01); the disease control rate of the observation group was 84.00%, higher than that of the control group (60.00%), and the difference was statistically significant (P<0.01); After treatment , levels of CEA, CA242,CA19-9 in observation group was lower than those in control group, and the difference was statistically significant (P<0.01); Adverse reactions after chemotherapy included nausea and vomiting, loss of appetite, fatigue, gastrointestinal reaction, liver damage, bone marrow suppression, hair loss, anemia and neutropenia; the incidences of fatigue and liver function damage in observation group were lower than those in control group with statistical differences (P<0.05), other adversereactions in the two groups had no statistically significant difference (P>0.05). **Conclusive:** Bevacizumab combined with chemotherapy in treatment of advanced colorectal cancer has the characteristics of good recent curative effect and high security, and it has very important reference value in clinic.

Key words: Advanced colorectal cancer; Chemotherapy; Bevacizumab

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前言

结直肠癌作为消化道常见的恶性肿瘤,多发于直肠或与乙状结肠的交界处,它是肠黏膜上皮细胞在遗传或其他特定的致癌环境下发生病变所导致。多数结直肠癌患者死于复发和转移,是严重威胁患者健康和生命质量的严重疾病,其发病率有逐年升高趋势[1]。晚期结直肠癌预后差,目前临床主要通过化疗来延长患者的生存时间和改善生命质量[2]。希罗达作为一种新的抗癌药物,可以明显提高疗效和延长患者寿命,但是研究发

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现其带来的副作用使很多患者难以承受从而中断治疗[3]。贝伐珠单抗作为分子靶向抗癌药物,研究发现它通过阻止和减弱血管内皮生长因子(vascular endothelial growth factor,VEGF)与血管内皮细胞表面受体的结合,抑制内皮细胞的有丝分裂从而阻止肿瘤细胞的生长,因此目前在临床应用较多[4,5]。笔者查阅国内相关文献发现关于两药联合使用的疗效及安全性研究的报道较少,本研究采用贝伐珠单抗体联合希罗达化疗晚期结直肠癌患者旨在探讨其临床疗效及安全性,为临床提供参考。

1 资料与方法

1.1 一般资料

收集 2010 年 2 月～2013 年 2 月我院肿瘤内科收治的晚期结直肠癌患者作为本试验对象,纳入标准:① 经病理组织学和细胞学检查确诊为晚期结直肠癌的患者;② 既往有放化疗史且停止放化疗 1 个月以上; ③ 生活质量卡氏评分 (KPS)≥ 60 分,且生存期预计≥ 3 个月者;④ 患者及家属知情同意,并签署知情书。排除标准:① 孕产妇、哺乳期妇女;② 合并有心功能不全者;③ 合并有肝肾功能障碍者;④ 有药物禁忌症者。

符合纳入标准的患者共 50 例, 按照随机数字表法将其均分为两组(各 25 例)。其中观察组男 14 例,女 11 例;年龄 36～79 岁,平均(55.4± 6.1)岁;结肠癌患者 8 例,直肠癌患者 17 例;组织学分级:G1 3 例,G2 14 例,G3 8 例;9 例 ECOG 功能评分 0～1 分,16 例 2 分;肝转移 7 例,肺转移 10 例,淋巴结转移 8 例。对照组男 12 例,女 13 例;年龄 33～76 岁,平均(56.3± 5.7)岁;结肠癌患者 10 例,直肠癌患者 15 例;组织学分级:G1 5 例,G2 13; 例,G3 7 例;11 例患者 ECOG 功能评分 0～1 分,14 例 2 分;肝转移者 5 例,肺转移者 13 例,淋巴结转移 7 例。两组一般资料的差异无统计学意义(P>0.05),具有可比性。

1.2 方法

化疗前均予以止吐等对症支持治疗, 两组均采用奥沙利铂,卡培他滨药物进行化疗,具体方法为:奥沙利铂 130 mg/m^2,卡培他滨 850 mg/m^2,每天两次口服,共持续服用 14 天,21 天重复。观察组在此基础上再联合贝伐珠单抗进行治疗,静脉滴注贝伐珠单抗 7.5 mg/kg d1。在化疗过程中出现手足综合征者在用药不会对研究结果产生影响的情况下口服维生素 B6 以及涂抹凡士林软膏。

1.3 疗效评价

⑴ 近期疗效评价按照 WHO 实体瘤的客观疗效评价标准[6]:① 完全缓解(complete response,CR):目标病灶全部消失,且肿瘤标志物正常;② 部分缓解(partial response,PR):基线病灶的直径总和缩小≥ 30%;③ 稳定(stable disease,SD):基线病灶直径总和所缩小但是未达 PR 或由增加但是未达 PD, 肿瘤标志物浓度没有变化;④ 进展(progressive disease,PD):基线病灶直径总和增加≥ 20%或出现新的病灶, 肿瘤标志物浓度增加。其中有效率 (RR) 为 CR+PR, 疾病控制率 (DCR)为 CR+PR+SD。⑵ 记录并比较治疗前后两组肿瘤标志物的浓度变化,包括癌胚抗原(CEA)、肿瘤相关黏液抗原(CA242)和糖链抗原 19-9(CA19-9)。⑶ 观察记录两组的不良反应发生率。

1.4 统计学处理

采用 SPSS19.0 统计软件进行数据的录入及统计分析,计量资料的描述采用($\bar{x}$± s)表示,两独立样本的比较采用 t 检验,治疗前后比较采用配对 t 检验,计数资料的描述采用率,比较采用 检验,P<0.05 表示差异有统计学意义。

2 结果

2.1 近期疗效评价

两组患者均完成至少 4 个周期的化疗, 观察组有效率为 56.00%,对照组 24.00%,观察组有效率高于对照组,差异有统计学意义 (P<0.01), 观察组的疾病控制率 84.00%, 对照组 60.00%,观察组高于对照组,差异有统计学意义(P<0.05)。见表 1。

2.2 治疗前后两组患者血清肿瘤标志物浓度比较

两组治疗前的 CEA、CA242、CA19-9 比较, 差异无统计学意义(P>0.05),两组治疗后的 CEA、CA242、CA19-9 浓度较治疗前下降,差异有统计学意义(P<0.01),观察组治疗后的 CEA、CA242、CA19-9 浓度低于对照组,差异有统计学意义(P<0.01)。见表 2。

表 1 两组患者近期临床疗效的比较

Table 1 Comparison of the recent curative effect in two groups

组别 Groups	例数 Cases	CR	PR	SD	PD	RR(%)	DCR(%)
观察组 Observation group	25	3	11	7	4	14(56.00※)	21(84.00△)
对照组 Control group	25	0	5	9	11	5(20.00)	14(56.00)

注:※)与对照组比较(=6.876,P=0.009);△)与对照组比较(=4.667,P=0.031)。

Note:※)compared with control group(=6.876,P=0.009);△) compared with control group(=4.667,P=0.031).

2.3 两组化疗后的不良反应情况比较

两组患者化疗后的主要不良反应有恶心、呕吐、食欲减低等胃肠道反应,乏力,肝功能损害,骨髓抑制,脱发,贫血以及中性粒细胞下降等,其中观察组的乏力,肝功能损害发生率低于对照组,差异有统计学意义(P<0.05),其余不良反应发生率两组差异无统计学意义(P>0.05)。见表 3。

3 讨论

结直肠癌作为临床常见且死亡率高的消化道恶性肿瘤,严重威胁人类的生命健康,早期肿瘤通过手术及术后的规范化辅助化疗可以明显延长患者寿命,提高生活质量[7,8]。但是对于晚期结直肠癌患者手术治疗的效果并不好,因此只能通过化疗来

表 2 治疗前后两组患者血清肿瘤标志物浓度变化($\bar{x}\pm s$)

Tabel 2 Serum tumor marker concentration changes of two group before and after treatment($\bar{x}\pm s$)

组别 Groups	例数 Cases	指标 Indexes	治疗前 Before treatment	治疗后 After treatment
观察组 Observation group	25	CEA(μg/L)	65.8± 13.9	17.0± 6.5△※
		CA242(IU/mL)	92.2± 22.7	30.6± 14.9△※
		CA19-9(kU、mL)	122.8± 37.6	31.2± 11.7△※
对照组 Control group	25	CEA(ug/L)	66.3± 14.5	37.4± 7.3△
		CA242(IU/mL)	91.5± 23.4	61.6± 15.5△
		CA19-9(kU、mL)	119.7± 38.0	43.4± 12.0△

注:△)与治疗前比较 P<0.01,※)与对照组比较 P<0.01。

Note:△)compared with before treatment P<0.01,※)compared with control groupP<0.01.

表 3 两组化疗后的不良反应情况

Table 3 Adverse reactions of two groups after chemotherapy

指标 Indexes	观察组 Observation group (%)	对照组 Control group(%)	X^2	P
恶心、呕吐 Nausea and vomiting	5(20.00)	8(32.00)	0.936	0.333
乏力 Fatigue	3(12.00)	10(40.00)	5.094	0.024
食欲减退 Loss of appetite	6(24.00)	11(44.00)	2.228	0.136
肝功能损害 Liver damage	3(12.00)	9(36.00)	3.947	0.047
骨髓抑制 Bone marrow suppression	2(8.00)	5(20.00)	1.495	0.221
脱发 Hair loss	3(12.00)	8(32.00)	2.914	0.088
手足综合征 Hand-foot syndrome	1(4.00)	2(8.00)	0.355	0.552
贫血 Anemia	3(12.00)	4(16.00)	0.166	0.684
中性粒细胞下降 Neutropenia	6(24.00)	7(28.00)	0.104	0.747

缓解患者的病情[9]。过去临床常用希罗达对晚期结直肠癌进行化疗,研究显示它对患者具有较好的疗效且生存期长,但是患者的耐受性差,不良反应多[10,11]。随着医学技术的不断发展,一种新的分子靶向药物贝伐珠单抗逐渐在临床上得到推广应用。其作用机制有[12]:⑴将 VEGF 作为作用的靶点,通过与内源性的 VEGF 竞争从而与 VEGF 受体进行结合,以抑制内皮细胞的有丝分裂使得肿瘤血管发生退化,同时阻止新生血管的生成,最后通过减少血液和氧气等对肿瘤生长的供应来限制肿瘤的继续生长;⑵通过降低内皮细胞的通透性从而促进化疗药物进入到肿瘤的组织中去,以提高化疗药物的浓度来提高化疗疗效。国外有研究表明贝伐珠单抗联用其他抗肿瘤药物治疗结直肠癌具有较好疗效且安全性高[15],但是作者查阅国内相关文献发现有关此类研究的文章还较少,本研究采用贝伐珠单抗联合奥沙利铂,希罗达化疗晚期结直肠癌,并以奥沙利铂,希罗达治疗的患者为对照组比较两组的临床疗效及耐受性。

结果显示,两组患者均完成了至少 4 个周期的化疗,观察组临床有效率为 56.00%高于对照组的 20.00%,差异有统计学意义,并且观察组的疾病控制率 84.00%也高于对照组的 56.00%,差异有统计学意义。说明贝伐珠单抗联合奥沙利铂,希罗达对晚期结直肠癌患者进行化疗的疗效优于单纯化疗组,且对晚期结直肠癌的疾病控制情况也优于单纯化疗组,, 这与有关研究结果一致[16]。此外研究还得出治疗后两组的血清肿瘤标志物浓度较治疗前下降,观察组治疗后的血清肿瘤标志物浓度低于对照组,进一步说明贝伐珠单抗联合奥沙利铂,希罗达治疗晚期结直肠癌的疗效较好,这与国外的研究结果一致[17]。可能是因为贝伐珠单抗通过促进肿瘤血管恢复到正常形态,降低了组织间隙的压力和血管的通透性,最终导致化疗药物进入肿瘤细胞的内部而升高了化疗药物的浓度,从而增强了化疗药物的抗肿瘤的功能[18]。本研究结果还得出化疗后两组患者的不良反应主要有恶心、呕吐、食欲减低等胃肠道反应,乏力,肝功能损害,骨髓抑制,脱发,贫血以及中性粒细胞下降等,其中观察组的乏力,肝功能损害发生率低于对照组,其余的不良反应发生率两组差异无统计学意义,这与有关研究得出的结果一致[19]。因此在化疗过程中应注意保肝护肝,避免损伤肝脏功能,同时因为贝伐株单抗联合奥沙利铂,希罗达的的不良反应小,患者的耐受性较好且对继续治疗的影响不大,因此在临床应用有重要意义[20]。

综上所述,贝伐株单抗联合希罗达化疗晚期结直肠癌具有

疗效好,患者的不良反应小且耐受性好等特点,临床有重要参考价值。

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