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西妥昔单抗和贝伐珠单抗治疗晚期结直肠癌的有效性和安全性比较*

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摘要 目的:比较西妥昔单抗和贝伐珠单抗治疗晚期结直肠癌的有效性和安全性。**方法:**选取 2014 年 1 月~2017 年 8 月我院收治的晚期结直肠癌患者 100 例,根据患者入院先后顺序随机分为两组,所有患者均给予 FOLFIRI 方案进行化疗,A 组在化疗的基础上给予贝伐珠单抗进行治疗,B 组在化疗的基础上给予西妥昔单抗进行治疗。比较两组患者临床治疗的缓解率、控制率及不良反应的发生情况,对所有患者随访 1 年,记录并比较两组患者的无进展生存期。**结果:**两组患者的缓解率、控制率、恶心呕吐、头晕、延迟性腹泻、肝肾损伤、白细胞减少、血小板减少和尿蛋白的发生率相比均无统计学差异($P>0.05$),但 B 组患者骨髓抑制和皮疹的发生率显著高于 A 组($P<0.05$);两组患者的无进展生存期相比无统计学差异($P>0.05$)。**结论:**西妥昔单抗和贝伐珠单抗治疗晚期结直肠癌的临床效果相当,且不良反应较轻,以 I~II 度为主,患者均可耐受,对症治疗均有所缓解。西妥昔单抗易引发骨髓抑制和皮疹,在临床应用过程中需注意并进行有效预防和积极处理。

关键词:西妥昔单抗;贝伐珠单抗;晚期结直肠癌;有效性;安全性

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Comparison of the Efficacy and Safety of Cetuximab and Bevacizumab in the Treatment of Advanced Colorectal Cancer*

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ABSTRACT Objective: To compare the efficacy and safety of cetuximab and bevacizumab in the treatment of advanced colorectal cancer. **Methods:** 100 patients with advanced colorectal cancer admitted to our hospital from January 2014 to August 2017 were selected and divided into two groups according to the sequence of admission. All the patients were treated with FOLFIRI for chemotherapy, group A was treated with bevacizumab on the basis of chemotherapy, and group B was treated with cetuximab on the basis of chemotherapy. The remission rate, control rate and incidence of adverse reactions were compared between the two groups. All patients were followed up for 1 year, and no progression-free survival was recorded and compared between the two groups. **Results:** There was no statistical difference in the remission rate and control rate between the two groups ($P>0.05$). In terms of adverse reactions, there were no statistically significant difference between the two groups in the incidence of nausea and vomiting, dizziness, delayed diarrhea, liver and kidney injury, leukopenia, thrombocytopenia and urinary protein ($P>0.05$), but the incidence of bone marrow suppression and rash in group B was significantly higher than that in group A ($P<0.05$). There was no statistically significant difference in the progression-free survival between the two groups ($P>0.05$). **Conclusion:** Cetuximab and bevacizumab had equal clinical effects in the treatment of advanced colorectal cancer. But cetuximab could easy cause bone marrow suppression and rash, which should be paid attention to in the process of clinical application and effective prevention and active treatment.

Key words: Cetuximab; Bevacizumab; Advanced colorectal cancer; Efficacy; Adverse reactions

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引言

结直肠癌是消化道常见的恶性肿瘤之一,其发病率在所有恶性肿瘤中排第三位,死亡率排第四位^[1-3]。近年来,随着社会的

不断进步和人们生活方式的改变,我国结直肠癌的发病率逐年上升,严重威胁患者的生命健康^[4]。由于该病早期没有典型的临床症状,起病比较隐匿,病情发展缓慢,大部分患者出现贫血、便血、乏力等症状后才被确诊,此时已发展为中晚期,具有转移

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的风险,且失去手术根治的机会^[5-7]。因此,药物治疗成为晚期结直肠癌患者治疗的主要手段。

临床治疗晚期结直肠癌的重点是提高治疗的效果,最大限度延长患者的生存期并改善患者的生存质量。化疗是目前临床对于晚期癌症常用的治疗方法,并取得了较好的临床效果^[8-10]。随着医学技术的不断发展,靶向药物相继应用于临床,该类药物以肿瘤细胞过表达的某些标志性分子为靶点,有针对性的作用于这些靶点,有效干预这些标志性分子的功能,从而达到抑制肿瘤的目的,具有较高的选择性、特异性及临床效果,但如果应用不当不仅会延误病情,还会给患者带来巨大的经济负担^[11-13]。目前,已发现的结直肠癌分子靶点主要有表皮生长因子受体、血管内皮生长因子及基质金属蛋白酶、选择性环氧合酶2等,其中研究较多的为表皮生长因子受体和血管内皮生长因子^[14-16]。西妥昔单抗是抗表皮生长因子受体的一种单克隆抗体,贝伐珠单抗是抑制血管内皮生长因子的单克隆抗体^[17,18]。本研究主要比较了西妥昔单抗和贝伐珠单抗治疗晚期结直肠癌的有效性和安全性,旨在为靶向药物的临床应用提供参考。

1 资料与方法

1.1 一般资料

选取2014年1月~2017年8月我院收治的晚期结直肠癌患者100例,纳入标准:①经病理学诊断为结直肠癌;②TNM分期均为IV期,无法手术治疗者;③入院时未接受化疗药物治疗者;④预计生存期超过6个月。排除标准:①合并其他恶性肿瘤或重大疾病者;②合并心、肝、肾等重要器官功能障碍者;③合并严重出血或血栓者;④有化疗禁忌者。根据患者入院先后顺序分为两组,A组50例,男28例,女22例;年龄38~70岁;平均 53.68 ± 3.54 岁;分化程度:低分化5例,中分化34例,高分化11例;粘液腺癌11例,腺癌33例,其他6例。B组50例,男27例,女23例;年龄36~71岁;平均 55.02 ± 3.78 岁;分化程度:低分化6例,中分化35例,高分化9例;粘液腺癌10例,腺癌33例,其他7例。两组患者一般资料比较差异无统计学意义($P>0.05$),具有可比性。

1.2 治疗方法

两组患者均给予FOLFIRI方案进行化疗,第1天,给予伊立替康(江苏恒瑞医药股份有限公司,国药准字H20061276)180 mg/m²,静脉滴注;第1~2天,每天给予5-氟尿嘧啶注射液

(亚宝药业集团股份有限公司,国药准字H20057995)600 mg/m²和四氢叶酸钙(赤峰蒙欣药业有限公司,国药准字H15021455)400 mg/m²,静脉滴注;每两周重复1次用药。A组在化疗的基础上给予贝伐珠单抗治疗,于化疗当天给予贝伐珠单抗注射液(Roche Pharma (Schweiz) Ltd,S20170035)10 mg/kg,与0.9%氯化钠注射液100 mL持续静脉滴注60分钟(第一次不得短于90分钟),每周一次,每两周重复1次用药。B组在化疗的基础上给予西妥昔单抗,于化疗当天给予西妥昔单抗注射液(Merck KGaA,S20171039)100 mg,与0.9%氯化钠注射液250 mL持续静脉滴注60分钟(第一次不得短于90分钟),每周一次,每两周重复1次用药。两组患者均接受4~6个治疗周期,治疗过程中出现不良反应均进行对症处理,治疗结束后7d对患者的临床效果进行评估。

1.3 观察指标

①临床疗效:根据RECIST1.0标准对两组患者的临床疗效进行评价,完全缓解(CR):全部病灶消失并至少维持4周;部分缓解(PR):病灶的最大径之和减少大于等于30%,并至少维持4周;稳定(SD):病灶的最大径之和减少小于30%,或增大未达到进展;进展(PD):病灶的最大径之和增加20%,或者出现新病灶。缓解率(ORR)=完全缓解率+部分缓解率;控制率(DCR)=完全缓解率+部分缓解率+稳定率。②并发症的发生情况:采用美国国家癌症研究所常见不良反应事件评定标准对两组患者的不良反应进行评价,包括恶心呕吐、头晕、延迟性腹泻、肝肾损伤、白细胞减少、血小板减少和尿蛋白等,分为0、I、II、III、IV度。③无进展生存期:采用门诊复查和电话等形式进行随访,随访时间为1年,了解患者的病情变化、死亡时间等。无进展生存期为从治疗开始至第一次出现进展或者死亡的时间。

1.4 统计学方法

采用SPSS 20.0进行数据分析,计量资料用 $\bar{x} \pm s$ 表示,组间比较行t检验;计数资料采用例和百分率表示,组间比较行 χ^2 检验,以 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 两组患者临床疗效比较

两组患者的缓解率和控制率相比均无统计学差异($P>0.05$),见表1。

表1 两组患者临床疗效比较[例(%)]

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

Group	n	CR	PR	SD	PD	ORR	DCR
Group A	50	6(12.00)	23(46.00)	10(20.00)	11(22.00)	29(58.00)	39(78.00)
Group B	50	4(8.00)	22(44.00)	9(18.00)	15(30.00)	26(52.00)	35(70.00)
χ^2	-	0.444	0.040	0.065	4.227	0.364	0.832
P	-	0.741	0.841	0.799	0.040	0.546	0.362

2.2 两组患者不良反应发生情况比较

两组患者恶心呕吐、头晕、延迟性腹泻、肝肾损伤、白细胞减少、血小板减少和尿蛋白相比均无统计学差异($P>0.05$),B

组患者的骨髓抑制和皮疹发生率显著高于对照组($P<0.05$),见表2。

表 2 两组患者不良反应发生率比较[例(%)]

Table 2 Comparison of the incidence of adverse reaction rate between the two groups[n(%)]

Group	Group A(n=50)				B(n=50)			
	0	I ~ II	III~IV	Summation	0	I ~ II	III~IV	Summation
CINV	24	21	5	26	27	18	5	23
Dizziness	39	8	3	11	40	8	2	10
Myelosuppression	37	13	0	13	27	20	3	23*
Neurovirulence	41	8	1	9	40	10	0	10
Delayed diarrhea	43	7	0	7	42	7	1	8
Liver and kidney Damage	37	11	2	13	35	12	3	15
Leukopenia	24	25	1	26	26	24	0	24
Thrombocytopenia	35	14	1	15	34	16	0	16
Urine protein	47	3	0	3	45	4	1	5
Erythra	47	2	1	3	37	9	4	13*

Note: Compared with Group A, * $P < 0.05$.

2.3 两组患者无进展生存期比较

A 组患者的无进展生存期为 9.58 ± 2.11 个月, B 组患者无进展生存期为 8.98 ± 2.04 个月, 两组比较无统计学差异($t=1.446, P=0.151$)。

3 讨论

对于晚期结直肠癌的治疗, 国际 NCCN 指南及中国卫生部的诊疗规范均推荐采用化疗联合靶向药物治疗^[19]。FOLFIRI 方案是治疗晚期结直肠癌常用的一种化疗方案, 伊立替康是一种高选择性的拓扑异构酶 I 抑制剂, 具有诱发 DNA 单链损伤的作用, 阻断 DNA 复制, 从而抑制肿瘤细胞^[20]。5- 氟尿嘧啶可抑制胸腺嘧啶核苷酸合成酶的活性, 阻断增殖期肿瘤细胞的活性而起到抑制肿瘤细胞的作用^[21]。四氢叶酸钙可增强 5- 氟尿嘧啶的作用, 同时加大对增殖期肿瘤细胞的杀伤力, 联合使用具有较好的临床效果^[22]。有研究显示^[23, 24]化疗联合靶向药物治疗可显著提高患者的无进展生存期和总生存期, 取得较好的临床效果, 但在实际应用的过程中存在一些问题, 如不同靶向药物的使用条件、不良反应不同, 价格昂贵、停药反弹等, 如何针对不同的患者选择安全有效的治疗方案已成为临床治疗的关键。研究显示约 70%~90% 的结直肠癌患者肿瘤组织中存在表皮生长因子受体高表达, 表皮生长因子受体对维持细胞的生长和增殖具有重要作用, 过度激活可诱导肿瘤的生长、侵袭和转移, 使得肿瘤进一步恶化^[25]。西妥昔单抗是人鼠嵌合型的单克隆抗体, 其作用靶点为肿瘤细胞过表达的表皮生长因子, 可有效抑制表皮生长因子信号通路的传导, 起到抑制肿瘤细胞增殖并诱导细胞凋亡的作用^[26, 27]。肿瘤的生长及转移需要丰富的血管, 贝伐珠单抗是一种人源性 IgG1 单克隆抗体, 为新型抗血管内皮生长因子靶向药物, 可直接阻断血管内皮生长因子与其受体的结合与活化, 抑制血管内皮细胞的增殖、从而抑制新生肿瘤血管的生成及肿瘤的生长和转移。还可以抑制肿瘤分化因子的血管生成效应, 改变肿瘤血管床、使肿瘤间质中的压力降低, 促进化疗药物有效释放进入肿瘤细胞而发挥较好的肿瘤作用^[28, 29]。

另外, 贝伐珠单抗还能够抑制肿瘤干细胞的增殖^[30]。因此, 本研究对比了西妥昔单抗和贝伐珠单抗治疗晚期结直肠癌的有效性和不良反应, 为临床应用提供参考。研究结果显示西妥昔单抗和贝伐珠单抗治疗结直肠癌的临床效果相当, 均可有效控制肿瘤的进展, 延长患者的无进展生存期。在不良反应方面, 西妥昔单抗骨髓抑制和皮疹的发生率高于贝伐珠单抗, 这可能是由于贝伐珠单抗的作用机制与化疗药物不同, 具有非细胞毒性和专一性的特点, 不良反应相对较少, 更适合与化疗药物联合使用^[31]。

综上所述, 西妥昔单抗和贝伐珠单抗治疗晚期结直肠癌的临床效果相当, 且不良反应较轻, 以 I ~ II 度为主, 患者均可耐受, 对症治疗均有所缓解。西妥昔单抗易引发骨髓抑制和皮疹, 在临床应用过程中需注意并进行有效预防和积极处理。

参考文献(References)

- [1] Arnold M, Sierra M S, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality [J]. Gut, 2017, 66 (4): 683-691
- [2] Tan D, Fu Y, Su Q, et al. Prognostic role of platelet-lymphocyte ratio in colorectal cancer: A systematic review and meta-analysis [J]. Medicine, 2016, 95(24): e3837
- [3] Mlecnik B, Bindea G, Angell H K, et al. Integrative Analyses of Colorectal Cancer Show Immunoscore Is a Stronger Predictor of Patient Survival Than Microsatellite Instability [J]. Immunity, 2016, 44(3): 698-711
- [4] Samawi H H, Shaheen A A, Tang P A, et al. Risk and predictors of suicide in colorectal cancer patients: a Surveillance, Epidemiology, and End Results analysis [J]. Current Oncology, 2017, 24 (6): e513-e517
- [5] Dienstmann R, Vermeulen L, Guinney J, et al. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer [J]. Nature Reviews Cancer, 2017, 17(2): 79-92
- [6] Huang Y Q, Liang C H, He L, et al. Development and validation of a radiomics nomogram for preoperative prediction of lymph node

- metastasis in colorectal cancer[J]. Science Foundation in China, 2016, 34(4): 2157-2164
- [7] Lech G, Słotwiński R, Słodkowski M, et al. Colorectal cancer tumour markers and biomarkers: Recent therapeutic advances [J]. World Journal of Gastroenterology, 2016, 22(5): 1745-1755
- [8] A Passardi, O Nanni, D Tassinari, et al. Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: final results for first-line treatment from the ITACa randomized clinical trial[J]. Annals of Oncology, 2016, 26(6): 1201-1207
- [9] Murcia O, Juárez M, Hernández-Illán E, et al. Serrated colorectal cancer: Molecular classification, prognosis, and response to chemotherapy [J]. World Journal of Gastroenterology, 2016, 22(13): 3516-3530
- [10] Mcquade R M, Stojanovska V, Bornstein J C, et al. Colorectal Cancer Chemotherapy: The Evolution of Treatment and New Approaches[J]. Current Medicinal Chemistry, 2017, 24(15): 1537-1557
- [11] Dong Z, Cui M Y, Peng Z, et al. Nanoparticles for Colorectal Cancer Targeted Drug Delivery and MR Imaging: Current Situation and Perspectives[J]. Current Cancer Drug Targets, 2016, 16(6): 536-550
- [12] Banerjee A, Pathak S, Devi S V, et al. Strategies for targeted drug delivery in treatment of colon cancer: current trends and future perspectives[J]. Drug Discovery Today, 2017, 22(8): 1224-1232
- [13] Wang J, Luo L, Wang D, et al. Combination Adjuvant Chemotherapy with Targeted Drugs for Treatment of Colorectal Cancer: A Network Meta-Analysis [J]. Journal of Cellular Biochemistry, 2018, 119(2): 1521-1537
- [14] Tomida C, Yamagishi N, Nagano H, et al. VEGF pathway-targeting drugs induce evasive adaptation by activation of neuropilin-1/cMet in colon cancer cells[J]. International Journal of Oncology, 2018, 52(4): 1350-1362
- [15] Zhang B, Fang C, Deng D, et al. Research progress on common adverse events caused by targeted therapy for colorectal cancer[J]. Oncology Letters, 2018, 16(1): 27-33
- [16] Limagne E, Euvrard R, Thibaudin M, et al. Accumulation of MDSC and Th17 cells in patients with metastatic colorectal cancer predict the efficacy of a FOLFOX-bevacizumab drug treatment regimen[J]. Cancer Research, 2016, 76(18): 5241-5252
- [17] Hong DS, Morris VK, El Osta B, et al. Phase IB Study of Vemurafenib in Combination with Irinotecan and Cetuximab in Patients with Metastatic Colorectal Cancer with BRAFV600E Mutation[J]. Cancer Discovery, 2016, 6(12): 1352-1365
- [18] A Passardi, O Nanni, D Tassinari, et al. Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: final results for first-line treatment from the ITACa randomized clinical trial[J]. Annals of Oncology, 2016, 26(6): 1201-1207
- [19] Williams C D, Grady W M, Zullig L L. Use of NCCN Guidelines, Other Guidelines, and Biomarkers for Colorectal Cancer Screening[J]. J Natl Compr Canc Netw, 2016, 14(11): 1479-1485
- [20] Hong DS, Morris VK, El Osta B, et al. Phase IB Study of Vemurafenib in Combination with Irinotecan and Cetuximab in Patients with Metastatic Colorectal Cancer with BRAFV600E Mutation[J]. Cancer Discovery, 2016, 6(12): 1352-1365
- [21] Toden S, Tran HM, TovarCamargo OA, et al. Epigallocatechin-3-gallate targets cancer stem-like cells and enhances 5-fluorouracil chemosensitivity in colorectal cancer [J]. Gastroenterology, 2016, 7(13): 16158-16171
- [22] Remuzgomartínez S, Genre F, Lópezmejías R, et al. Decreased expression of methylene tetrahydrofolate reductase (MTHFR) gene in patients with rheumatoid arthritis [J]. Clinical & Experimental Rheumatology, 2016, 34(1): 106-110
- [23] Yano S. Combined Therapy with Targeted Drugs in Lung Cancer[J]. Gan to Kagaku Ryoho Cancer & Chemotherapy, 2016, 43 (4): 413-418
- [24] Wang J, Luo L, Wang D, et al. Combination Adjuvant Chemotherapy with Targeted Drugs for Treatment of Colorectal Cancer: A Network Meta-Analysis [J]. Journal of Cellular Biochemistry, 2018, 119(2): 1521-1537
- [25] Yadav M, Singh A K, Kumar H, et al. Epidermal growth factor receptor inhibitor cancer drug gefitinib modulates cell growth and differentiation of acute myeloid leukemia cells via histamine receptors[J]. Biochim Biophys Acta, 2016, 1860(10): 2178-2190
- [26] Hung-Chih H, Kien T T, Lu Y J, et al. Mutations of KRAS/NRAS/BRAF predict cetuximab resistance in metastatic colorectal cancer patients[J]. Oncotarget, 2016, 7(16): 22257-22270
- [27] Magrini S M, Buglione M, Corvò R, et al. Cetuximab and Radiotherapy Versus Cisplatin and Radiotherapy for Locally Advanced Head and Neck Cancer: A Randomized Phase II Trial[J]. Journal of Clinical Oncology, 2016, 34(5): 427-435
- [28] Arevalo J F, Lasave A F, Wu L, et al. Intravitreal bevacizumab for diabetic macular oedema: 5-year results of the Pan-American Collaborative Retina Study group [J]. British Journal of Ophthalmology, 2016, 100(12): 1605-1610
- [29] Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial[J]. Lancet, 2016, 387(10026): 1405-1414
- [30] Hahn N M, Stadler W M, Zon R T, et al. Phase II Trial of Cisplatin, Gemcitabine, and Bevacizumab As First-Line Therapy for Metastatic Urothelial Carcinoma: Hoosier Oncology Group GU 04-75[J]. Journal of Clinical Oncology, 2016, 29(12): 1525-1530
- [31] Tewari K S, Sill M W, Penson R T, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240)[J]. Lancet, 2017, 390(10103): 1654-1663