doi: 10.13241/j.cnki.pmb.2017.04.020

曲妥珠单抗联合 SOX 方案治疗 HER-2 阳性晚期胃癌的临床疗效观察

曹冉华 苏乌云△ 呼 群 刘彩霞 赵海燕

(内蒙古医科大学附属医院肿瘤内科 内蒙古 呼和浩特 010050)

摘要 目的:探讨曲妥珠单抗联合替吉奥和奥沙利铂(SOX 方案)治疗人类表皮生长因子受体 -2(HER-2)阳性晚期胃癌的临床疗效。**方法**:选择 2014 年 2 月到 2016 年 2 月在我院收治的 48 例 HER-2 阳性晚期胃癌患者,随机分为实验组和对照组,各 24 例。对照组患者给予 SOX 化疗方案,实验组患者给予曲妥珠单抗联合 SOX 化疗方案,两组患者均给予治疗 3 个疗程。评价并比较两组患者临床疗效。比较两组患者治疗后不良反应发生情况。检测并比较两组患者治疗前后血清糖类抗原 125(CA125)、癌胚抗原(CEA)及组织多肽特异性抗原(TPS)水平。**结果**:实验组患者的有效率(RR)为 58.33%、疾病控制率(DCR)为 87.50%,均明显高于对照组患者的 29.17%和 45.83%,差异具有统计学意义(P<0.05)。治疗后两组患者血清 CA125、CEA 及 TPS 水平均明显低于治疗前,且实验组患者上述各指标均明显低于对照组,差异具有统计学意义(P<0.05)。两组患者不良反应发生率比较差异均无统计学意义(P>0.05)。**结论**:曲妥珠单抗联合 SOX 方案治疗 HER-2 阳性晚期胃癌患者临床疗效显著,能够明显降低血清 CA125、CEA 及 TPS 水平,不良反应发生率低,值得在临床上推广应用。

关键词:曲妥珠单抗;替吉奥;奥沙利铂;胃癌;人类表皮生长因子受体 -2

中图分类号:R735.2 **文献标识码**:A **文章编号**:1673-6273(2017)04-680-04

Clinical Observation of Trastuzumab Combined with SOX Regimen in the Treatment of HER-2 Positive Advanced Gastric Cancer

CAO Ran-hua, SU Wu-yun△, HU Qun, LIU Cai-xia, ZHAO Hai-yan

(Department of Oncology, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia, 010050, China)

ABSTRACT Objective: To study the clinical efficacy of trastuzumab combined with SOX regimen in the treatment of HER-2 positive advanced gastric cancer. **Methods:** A total of 48 patients with HER2-positive advanced gastric cancer treated in our hospital from February 2014 to February 2016 were selected. They were divided into control group (n=24) and experiment group (n=24) randomly. The control group were treated with the SOX chemotherapy regimens, the experiment group were treated with trastuzumab combined with SOX chemotherapy regimens, the two groups were treated for 3 months. The clinical efficacy of the two groups were compared. The adverse reactions of the two groups were compared after treatment. The serum CA125, CEA and TPS level of the two groups were compared before and after treatment. **Results:** The RR of the experiment group was 58.33%, the DCR was 87.50%, which were significantly higher than 29.17% and 45.83% in the control group, the differences were statistically significant (P<0.05). The serum CA125,CEA and TPS level of the two groups after treatment were significantly lower than that before treatment (P<0.05), and that of experiment group were significantly lower than the control group, the differences were statistically significant (P<0.05). There were no significantly differences of the adverse effects rates in the two groups after treatment (P>0.05). **Conclusion:** The clinical efficacy of trastuzumab combined with SOX regimen in the treatment of advanced gastric cancer patients is significant, which can significantly reduce the serum CA125CEA and TPS levels, the incidence of adverse reactions is low, so it is worthy clinical application.

Key words: Trastuzumab,S-1; Oxaliplatin; Gastric cancer; Hunman epidermal growth factor receptor-2

Chinese Library Classification(CLC): R735.2 Document code: A

Article ID: 1673-6273(2017)04-680-04

前言

胃癌是一种临床常见的消化道恶性肿瘤,在我国的发病率居于恶性肿瘤的第三位[1]。随着生活节奏的加快和饮食结构的转变,胃癌的发病率有逐年增高的趋势,严重威胁着人们的身体健康[2]。由于胃癌在发病初期并无典型的临床症状和病理特征,大多数患者在医院确诊时往往已处于病理晚期,生存期较短且预后较差[3,4]。有研究发现[5],25%-30%的晚期胃癌患者表现出人类表皮生长因子受体 -2(human epidermal growth factor receptor-2,HER-2)表达阳性。HER-2 基因属于 HER 家族,主要调控肿瘤的生长、浸润及转移[6]。HER-2 阳性晚期胃癌患者的治疗思路主要采用作用于 HER-2 靶点的抗癌药物联合 COX 化疗方案。曲妥珠单抗是一个新型的以 HER-2 癌基因为靶点的人源化单克隆抗体,对 HER-2 癌基因受体有极高的选择特异

作者简介:曹冉华(1980-),女,硕士,副主任医师,从事肿瘤学方面的研究,E-mail:caoranhua202015@sina.com

△ 通讯作者:苏乌云(1963-),女,硕士,主任医师,从事肿瘤学方面的研究

(收稿日期:2016-06-29 接受日期:2016-07-25)

性,特异性可抑制 HER-2 蛋白的表达,从而抑制肿瘤的生长[7]。本研究探讨曲妥珠单抗联合替吉奥和奥沙利铂(SOX 方案)治疗晚期胃癌且 HER-2 阳性患者的临床疗效,研究结果如下。

1 资料与方法

1.1 一般资料

选择 2014 年 2 月到 2016 年 2 月在我院收治的 48 例晚期胃癌患者作为研究对象。病例纳入标准:⑴ 经病理学确诊为胃癌患者;⑵ TNM 分期为 IV 期患者;⑶ 经免疫组化检测为 HER-2 表达阳性;⑷ 至少有一个可测量的病灶;⑸ karnofsky 评分≥ 60 分;⑹ 预计生存期≥ 3 个月。病例排除标准:⑴ 合并有其他恶性肿瘤患者;⑵ 不配合治疗患者;⑶ 肝、肾功能不全患者;⑷ 有严重感染性疾病患者;⑸ 无可测量病灶患者;⑹ 有化疗禁忌症患者。按随机数字表法将 48 例入选患者随机分为对照组(24 例)和实验组(24 例)。对照组患者,男 15 例,女 9 例;年龄 39-70 岁,平均年龄(60.39± 8.10)岁;体重 47-72kg,平均体重(53.14± 12.31)kg;肿瘤类型:低分化腺癌 11 例、中分化腺癌 6 例、黏液性腺癌 5 例、印戒细胞癌 2 例;转移部位:肺转移 4 例、肝转移 8 例、腹腔淋巴结转移 8 例、全身多发转移 4 例。实验组患者,男 16 例,女 8 例;年龄 38-71 岁,平均年龄(61.24± 9.43)岁;体重 45-71kg,平均体重(52.68± 13.92)kg;肿瘤类型:低分化腺癌 11 例、中分化腺癌 8 例、黏液性腺癌 3 例、印戒细胞癌 2 例;转移部位:肺转移 3 例、肝转移 7 例、腹腔淋巴结转移 9 例、全身多发转移 5 例。两组患者的一般资料,包括性别、年龄、体重、肿瘤类型及转移部位等比较差异均无统计学意义(P>0.05),具有可比性。所有患者均知情同意且自愿加入本研究,并经医院伦理委员会批准。

1.2 实验方法

对照组患者给予 SOX 化疗方案,具体为:替吉奥(S-1,购自山东新时代药业有限公司,20 mg/ 粒,国药准字 H20080802),早、晚饭后口服,2 次 /d,d1-14,服用剂量按照患者体表面积调整,调整方案为[8]:S 体表 <1.25 m^2 者,40 mg/ 次;1.25 m^2≤ S 体表 <1.50 m^2 者,50 mg/ 次;S 体表≥ 1.25 m^2 者,60 mg/ 次;奥沙利铂(购自江苏恒瑞医药股份有限公司,50 mg/ 支,国药准字 H20000337),静脉滴注,130 mg/m^2,d1,每 21 d 重复 1 次,重复 1 次为 1 个疗程。实验组患者在 SOX 化疗方案的基础上,给予曲妥珠单抗(购自上海罗氏制药有限公司,440 mg/ 瓶,批准文号:S20060026)。曲妥珠单抗,静脉滴注,首次 4 mg/kg,此后剂量减半,1 次 /w。两组患者均给予治疗 3 个疗程。

1.3 检测指标

1.3.1 临床疗效评价 依据 2000 年美国癌症研究中心制定的实体瘤疗效评价标准[9],临床疗效分为:⑴ 完全缓解(complete remission, CR):病灶完全消失,临床症状完全缓解,时间不少于 1 月;⑵ 部分缓解(partial remission, PR):病灶面积缩小 50%以上,临床症状有所缓解,时间不少于 1 月;⑶ 疾病稳定(stable disease, SD):病灶面积基本无变化,临床症状无变化,时间不少于 1 月;⑷ 疾病进展(progression disease, PD):病灶面积增大超过 20%,甚至发生转移,临床症状明显加重。有效率(response rate, RR)=(CR+PR)/(CR+PR+SD+PD)× 100%,疾病控制率(disease control rate, DCR)=(CR+PR+SD)/(CR+PR+SD+PD)× 100%。

1.3.2 血清肿瘤标志物水平检测 两组患者均于治疗前后清晨空腹采集静脉血 5 mL,以 3000 rpm 离心 10 min 以分离血清,检测并比较治疗前后血清糖类抗原 125(cancer antigen 125,CA125)、癌胚抗原(carcinoembryonic antigen, CEA)及组织多肽特异性抗原(tissue polypeptide specific antigen,TPS)水平。血清 CA125 水平的检测采用双抗夹心酶联免疫(ELISA)法检测试剂盒,所用试剂及检测试剂盒均购自杭州华得森生物技术有限公司,所有操作均严格按照试剂盒所附说明书进行;血清 CEA 和 TPS 的水平采用电化学发光微粒子免疫分析法检测,所用仪器为购自美国贝克曼公司的 AIA-1800 型全自动酶免疫分析仪。

1.4 数据处理

本研究结果数据的处理采用 SPSS19.0 软件包,计数资料采用 X^2 检验,以率(%)表示,计量资料采用方差 t 检验,以均数± 标准差($\bar{x}$± s)表示,P<0.05 表示差异具有统计学意义。

2 结果

2.1 临床疗效比较

实验组患者的 RR 为 58.33%、DCR 为 87.50%,均明显高于对照组患者的 29.17%和 45.83%,差异具有统计学意义(P<0.05)。见表 1。

表 1 两组患者临床疗效比较

Table 1 Comparison of the clinical efficacy of the two groups

Groups	n	CR	PR	SD	PD	RR /%	DCR /%
Control group	24	1	6	4	13	7(29.17)	11(45.83)
Experiment group	24	3	11	7	3	14(58.33)	21(87.50)
X^2 value						4.840	5.828
P value						0.028	0.016

2.2 血清 CA125、CEA 及 TPS 水平比较

治疗前,两组患者血清 CA125、CEA 及 TPS 水平比较差异无统计学意义(P>0.05);治疗后,两组患者血清 CA125、CEA 及 TPS 水平均明显低于治疗前,同时实验组患者上述各血清肿瘤标志物水平均明显低于对照组(P<0.05)。见表 2。

表 2 两组患者血清 CA125、CEA 及 TPS 水平比较

Table 2 Comparison of serum CA125, CEA and TPS levels of the two groups

Groups	n	Time	CA125(U/mL)	CEA(mg/mL)	TPS (IU/mL)
Control group	24	Before treatment	62.33± 11.72	10.93± 3.26	461.25± 97.45
		After treatment	29.48± 7.32*	7.05± 2.12*	341.47± 82.40*
Experiment group	24	Before treatment	61.85± 12.05	11.14± 2.98	459.68± 104.33
		After treatment	11.34± 4.64*#	4.86± 1.67*#	187.51± 53.48*#

Note: Compared with the same group before treatment, *P<0.05; Compared with the contorl group, #P<0.05.

2.3 不良反应比较

治疗后，两组患者的不良反应发生率（包括肝功能损伤、骨髓抑制、周围神经毒性、消化道反应、心脏毒性等）比较，差异均无统计学意义（P>0.05）。见表 3。

表 3 两组患者治疗后不良反应比较[n(%)]

Table 3 Comparison of incidence of adverse reactions between the two groups[n(%)]

Groups	n	Liver injury	Bone marrow inhibition	Peripheral nerve toxicity	Gastrointestinal reaction	Cardiac toxicity
Control group	24	4(16.67)	16(66.67)	10(41.67)	8(33.33)	2(8.33)
Experiment group	24	3(12.50)	14(58.33)	9(37.50)	7(29.17)	1(4.17)
X2 value		0.143	0.133	0.053	0.067	0.333
P value		0.705	0.715	0.819	0.796	0.564

3 讨论

晚期胃癌具有较低的生存率，术后 5 年生存率仅为 20%左右[10]。目前，对于晚期胃癌的治疗在医学界尚未建立统一的有效治疗方案。近年来，有文献报道，对晚期胃癌患者采用奥沙利铂联合替吉奥的 SOX 化疗方案，总有效率达 59%，疾病治愈率达到 84%[11,12]。曲妥珠单抗是一个新型的基于 HER-2 癌基因为靶点的单克隆抗体，其衍生自鼠单抗 4D5，能够通过介导细胞毒性作用来发挥抑制癌细胞增殖的作用[13,14]。HER-2 癌基因介导磷脂酰肌醇 3 激酶（PI3K）- 蛋白激酶 B 通路，能够通过调节细胞凋亡因子来调控肿瘤细胞的增殖和侵袭[15]。有文献报道[16]，HER-2 的表达与胃癌的病理分期、进展及转移有一定的相关性。本研究通过联合应用曲妥珠单抗和 SOX 化疗方案来治疗 HER-2 阳性晚期胃癌患者，探讨其临床疗效及对血清肿瘤标志物 CA125、CEA 及 TPS 水平的影响，以期为临床选用合理有效的化疗方案来治疗 HER-2 阳性晚期胃癌患者提供一定的临床依据。

本研究结果显示，实验组患者的 RR 为 58.33%、DCR 为 87.50%，均明显高于对照组患者的 29.17%和 45.83%，差异具有统计学意义。提示曲妥珠单抗联合 SOX 化疗方案治疗 HER-2 阳性晚期胃癌的临床疗效显著。这可能是由于曲妥珠单抗是一种新型的分子靶向治疗药物，其特异性作用于 HER-2 阳性晚期胃癌患者的 HER-2 癌基因，通过抑制其表达来抑制癌细胞的增殖和转移[17]。这种新型的特异性极高的蛋白质分子联合 SOX 化疗方案具有协同抑制癌细胞和杀灭癌细胞的作用，具有较好的临床疗效。本研究结果显示，治疗前，两组患者血清 CA125、CEA 及 TPS 水平比较差异无统计学意义（P>0.05）；治疗后，两组患者血清 CA125、CEA 及 TPS 水平均明显低于治疗前，同时实验组患者上述各血清肿瘤标志物水平均明显低于对照组，差异具有统计学意义（P<0.05）。提示曲妥珠单抗联合 SOX 化疗方案能明显降低 HER-2 阳性晚期胃癌患者血清中肿瘤标志物 CA125、CEA 及 TPS 水平。CA125 是一种广谱的癌症血清肿瘤标志物，有研究发现，血清 CA125 水平随胃癌的进展逐渐升高[18]。CEA 在子宫内膜癌、肺癌、卵巢癌等多种恶性肿瘤组织中均有表达，在胃癌中的灵敏度为 30%左右，随胃癌细胞的增殖和胃癌的转移，血清中的水平有明显增高[19]。TPS 在胃癌组织中高表达，随肿瘤恶性程度，在肿瘤组织中的表达增高[20]。另外本研究结果显示，治疗后，两组患者的不良反应发生率（包括肝功能损伤、骨髓抑制、周围神经毒性、消化道反应、心脏毒性等）比较均无统计学意义（P>0.05）。提示曲妥珠单抗联合 SOX 化疗方案治疗 HER-2 阳性晚期胃癌患者的不良反应发生率较低，安全性较好。

综上所述，曲妥珠单抗联合 SOX 方案治疗 HER-2 阳性晚期胃癌患者临床疗效显著，能够明显降低血清 CA125、CEA 及 TPS 水平，不良反应发生率低，值得在临床上推广应用。

参考文献（References）

[1] Kataoka H, Mori Y, Shimura T, et al. A phase II prospective study of the trastuzumab combined with 5-weekly S-1 and CDDP therapy for HER2-positive ad vanced gastric cancer [J].Cancer Chemother Pharmacol, 2016, 77(5): 957-962

[2] Zhou J, Peng Z, Liu Y, et al. Erratum to:Predictive value of serum HER2 ECD in patients with HER2-positive advanced gastric cancer treated with trastuzumab plus chemotherapy[J]. J Gastroenterol,2016, 51(5): 509-510

[3] Zhou J, Peng Z, Liu Y, et al. Predictive value of serum HER2 ECD in patients with HER2-positive advanced gastric cancer treated with trastuzumab plus chemotherapy [J]. J Gastroenterol, 2015, 50 (9): 955-961

[4] Kim YS, Sym SJ, Baek MY, et al. Low-dose capec itabine plus

trastuzumab as first-line treatment in patients 75 years of age or older with HER2-positive advanced gastric cancer:a pilot study [J]. Cancer Chemother Pharmacol, 2015, 76(6): 1267-1272

[5] Liu B, Ying J, Luo C, et al. S-1 combined with oxaliplatin as first line chemotherapy for Chinese advanced gastric cancerpatients [J]. Hepatogastroenterology, 2012, 59(114): 649-653

[6] Chua C, Tan IB, Yamada Y, et al. Phase II study of trastuzumab in combination with S-1 and cisplatin in the first-line treatment of human epidermal growth factor receptor HER2-positive advanced gastric cancer [J]. Cancer Chemother Pharmacol, 2015, 76 (2): 397-408

[7] Ock CY, Lee KW, Kim JW, et al. Optimal Patient Selection for Trastuzumab Treatment in HER2-Positive Advanced Gastric Cancer [J]. Clin Cancer Res, 2015, 21(11): 2520-2529

[8] Kim GM, Jeung HC, Rha SY, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer[J]. Eur J Cancer, 2012, 48(4): 518-526

[9] Kang YK, Rha SY, Tassone P, et al. A phase IIa dose-finding and safety study of first-line pertuzumab in combination with trastuzumab, capecitabine and cisplatin in patients with HER2-positive advanced gastric cancer[J]. Br J Cancer, 2014, 111(4): 660-666

[10] Lu Y, Liu Z, Zhang J. S-1 plus oxaliplatin vs.S-1 as first-line treatment in patients with previously untreated advanced gastric cancer: a randomized phase II study [J]. J Chemother, 2014, 26(3): 159-164

[11] Sanford M. Trastuzumab: a review of its use in HER2-positive advanced gastric cancer[J]. Drugs, 2013, 73(14): 1605-1615

[12] Zhong DT, Wu RP, Wang XL, et al. Combination Chemotherapy with S-1 and Oxaliplatin (SOX)as First-Line Treatment in Elderly Patients with Advanced Gastric Cancer [J]. Pathol Oncol Res, 2015, 21(4): 867-873

[13] Zhu B, Wu JR, Zhou XP. A Retrospective Comparison of Trastuzumab Plus Cisplatin and Trastuzumab Plus Capecitabine in Elderly HER2-Positive Advanced Gastric Cancer Patients [J]. Medicine(Baltimore), 2015, 94(34): e1428

[14] Nishino M, Hosoda Y, Okano M, et al. A Case of HER2-Positive Advanced Gastric Cancer with a Pathological Complete Response to Neoadjuvant Chemotherapy with S-1/CDDP/Trastuzumab[J]. Gan To Kagaku Ryoho, 2015, 42(12): 2043-2045

[15] Endo S, Yamada T, Okuyama M, et al. A case of HER2-positive advanced gastric cancer successfully treated via capecitabine, cisplatin,and trastuzumab combination chemotherapy [J]. Gan To Kagaku Ryoho, 2015, 42(3): 359-361

[16] Gomez-Martin C, Plaza JC, Pazo-Cid R, et al. Level of HER2 gene amplification predicts response and overall survival in HER2-positive advanced gastric cancer treated with trastuzumab [J]. J Clin Oncol, 2013, 31(35): 4445-4452

[17] Honma Y, Shimada Y, Takashima A, et al. Efficacy of S-1 plus cisplatin combination chemotherapy in patients with HER2-positive advanced gastric cancer[J]. Int J Clin Oncol, 2014, 19(5): 863-870

[18] Kim JH, Jun KH, Jung H, et al. Prognostic Value of Preoperative Serum Levels of Five Tumor Markers (Carcinoembryonic Antigen, CA19-9, Alpha-fetoprotein, CA72-4, and CA125)in Gastric Cancer [J]. Hepatogastroenterology, 2014, 61(131): 863-869

[19] Huang ZB, Zhou X, Xu J, et al. Prognostic value of preoperative serum tumor markers in gastric cancer [J]. World J Clin Oncol, 2014, 5(2): 170-176

[20] Aurello P, Sagnotta A, Terrenato I, et al. Oncologic value of laparoscopy-assisted distal gastrectomy for advanced gastric cancer:A systematic review and meta-analysis [J]. J Minim Access Surg,2016, 12(3): 199-208

（上接第 768 页）

[13] Chen F, Ni YC. Magnetic resonance diffusion-perfusion mismatch in acute ischemic stroke: An update [J]. World Journal of Radiology, 2012, 4(3): 63-74

[14] Richardson JD, Baker JM, Morgan PS, et al. Cerebral perfusion in chronic stroke: implications for lesion-symptom mapping and functional MRI[J]. Behavioural Neurology, 2011, 24(2): 117-122

[15] Fridriksson J, Richardson JD, Fillmore P, et al. Left hemisphere plasticity and aphasia recovery[J]. Neuroimage, 2012, 60(2): 854-863

[16] Turkeltaub PE, Messing S, Norise C, et al. Are networks for residual language function and recovery consistent across aphasic patients? [J]. Neurology, 2011, 76(20): 1726-1734

[17] Zubicaray GI, Rose SE, McMahon KL. The structure and connectivity of semantic memory in the healthy older adult brain[J]. Neuroimage, 2011, 5(24): 1488-1494

[18] Lindenberg R, Zhu LL, Ruber T, et al. Predicting functional motor potential in chronic stroke patients using diffusion tensor imaging[J]. Human Brain Mapping, 2012, 33(5): 1040-1051

[19] Nunnari D, Bonanno L, Bramanti P, et al. Diffusion Tensor Imaging and Neuropsychologic Assessment in Aphasic Stroke [J]. J Stroke Cerebrovasc Dis, 2014, 23(10): e477-e478

[20] Wang J, Marchina S, Norton AC, et al. Predicting speech fluency and naming abilities in aphasic patients[J]. Front Hum Neurosci, 2013, 7: 831

[21] Kim SH, Jang SH. Prediction of aphasia outcome using diffusion tensor tractography for arcuate fasciculus in stroke [J]. Am J Neuroradiol, 2013, 34(4): 785-790

[22] Allendorfer JB, Kissela BM, Holland SK, et al. Different patterns of language activation in post-stroke aphasia are detected by overt and covert versions of the verb generation fMRI task [J]. Med Sci Monit, 2012, 18(3): 135-137

[23] Fridriksson J, Richardson JD, Fillmore P, et al. Left hemisphere plasticity and aphasia recovery[J]. Neuroimage, 2012, 60(2): 854-863

[24] Elkana O, Frost R, Kramer U, et al. Cerebral language reorganization in the chronic stage of recovery: a longitudinal fMRI study[J]. Cortex, 2013, 49(1): 71-81

[25] Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult [J]. Brain, 2011, 134: 2197-2221