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消癌平注射液联合表柔比星新辅助化疗对三阴性乳腺癌患者免疫功能、生活质量及血清肿瘤标志物的影响*

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摘要 目的:探讨消癌平注射液联合表柔比星新辅助化疗对三阴性乳腺癌(TNBC)患者免疫功能、生活质量及血清肿瘤标志物的影响。**方法:**选取 TNBC 患者 89 例,按照随机数字表法分为对照组和研究组,对照组(n=44)患者给予表柔比星新辅助化疗治疗,研究组(n=45)患者给予消癌平注射液联合表柔比星新辅助化疗。对比两组疗效、免疫功能、生活质量、血清肿瘤标志物及不良反应。**结果:**研究组治疗 12 周后的临床总有效率为 91.11%(41/45),高于对照组的 63.64%(28/44)($P<0.05$)。两组治疗 12 周后健康调查简表(SF-36)量表各维度评分升高,且研究组较对照组高($P<0.05$)。两组治疗 12 周后 CD4⁺CD25⁺Treg、Th17/Treg 均降低,且研究组较对照组低($P<0.05$),Th17 升高,且研究组较对照组高($P<0.05$)。两组治疗 12 周后癌胚抗原(CEA)、糖类抗原 199(CA199)、糖类抗原 125(CA125)均降低,且研究组较对照组低($P<0.05$)。两组不良反应发生率对比未见差异($P>0.05$)。**结论:**消癌平注射液联合表柔比星新辅助化疗治疗 TNBC,具有确切的治疗效果,可降低血清肿瘤标志物水平,改善患者免疫功能和生活质量。**关键词:**消癌平注射液;表柔比星;化疗;三阴性乳腺癌;免疫功能;生活质量;肿瘤标志物
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Effect of Xiaoaiping Injection Combined with Epirubicin Neoadjuvant Chemotherapy on Immune Function, Quality of Life and Serum Tumor Markers in Triple Negative Breast Cancer Patients*

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ABSTRACT Objective: To investigate the effect of xiaoaping injection combined with epirubicin neoadjuvant chemotherapy on immune function, quality of life and serum tumor markers in patients with triple negative breast cancer (TNBC). **Methods:** 89 patients with TNBC were selected, and divided into control group and study group by random number table method. The control group (n=44) was given epirubicin neoadjuvant chemotherapy, while the study group (n=45) was given xiaoaping injection combined with epirubicin neoadjuvant chemotherapy. The efficacy, immune function, quality of life, serum tumor markers and adverse reactions were compared between two groups. **Results:** The clinical total effective rate of the study group at 12 weeks after treatment was 91.11%(41/45), which was higher than 63.64%(28/44) of the control group ($P<0.05$). 12 weeks after treatment, 36-item short form (SF-36) scores of all dimension of the two groups increased, and the study group was higher than the control group ($P<0.05$). 12 weeks after treatment, CD4⁺CD25⁺Treg and Th17/Treg in the two groups were decreased, and the study group was lower than the control group($P<0.05$), and Th17 was increased, and the study group was higher than the control group ($P<0.05$). 12 weeks after treatment, the levels of carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199) and carbohydrate antigen 125 (CA125) in the two groups were decreased, and the study group was lower than the control group ($P<0.05$). There was no difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Xiaoaiping injection combined with epirubicin neoadjuvant chemotherapy in the treatment of TNBC has definite therapeutic effect, reduces serum tumor marker level, improves immune function and quality of life of patients.

Key words: Xiaoaiping injection; Epirubicin; Neoadjuvant chemotherapy; Triple negative breast cancer; Immune function; Quality of life; Tumor markers

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前言

乳腺癌是女性的常见恶性肿瘤,而三阴性乳腺癌(Triple negative breast cancer, TNBC)是乳腺癌的一种特殊亚型,以缺

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乏人表皮生长因子受体-2以及孕、雌激素受体表达为临床特征,约占所有乳腺癌患者的15%~20%^[1-3]。目前临床对TNBC的治疗多采用化疗、放疗等措施,新辅助化疗是指紫杉类联合蒽环类化疗药物的新型化疗方法,临床常应用表柔比星新辅助化疗治疗TNBC^[4,5],但部分患者化疗后不良反应较多,降低化疗效果,因此,临床急需寻找更为合理有效的化疗方案。消癌平注射液是中草药乌骨藤提取物的商品名,内含多种生物碱、多糖及皂苷等抑制肿瘤的有效成分,可有效阻止肿瘤疾病进展^[6,7]。本院针对TNBC患者给予消癌平注射液联合表柔比星新辅助化疗,疗效较好,总结如下。

1 资料与方法

1.1 一般资料

选取2018年3月~2020年3月我院收治的89例TNBC患者,研究通过我院伦理学委员会批准进行。采用随机数字表法分为对照组、研究组,其中对照组44例,年龄28~65(42.16±5.38)岁;体质量指数20~27(23.85±0.97)kg/m²;临床分期:II期20例,III期24例;病灶直径3~6(4.82±0.21)cm。研究组45例,年龄26~67(42.23±4.71)岁;体质量指数20~27(23.36±0.81)kg/m²;临床分期:II期19例,III期26例;病灶直径3~6(4.76±0.23)cm。两组一般资料对比无差异($P>0.05$),具有可比性。

1.2 纳入排除标准

纳入标准:(1)雌、孕激素受体、人类表皮生长因子受体2表达阴性和(或)荧光原位杂交HER2/Neu基因无扩增,经病理组织学诊断为TNBC;(2)年龄≥18周岁的女性患者;(3)患者及其家属知情本研究且签署同意书;(4)诊断标准参考《中国抗癌协会乳腺癌诊治指南与规范(2013版)》^[8];(5)患者预计生存时间>6个月;(6)患者入院前未接受过其他治疗。排除标准:(1)重要脏器功能受损者;(2)合并其他恶性肿瘤者;(3)依从性差、有精神疾患不能配合诊疗者;(4)非医疗原因退出试验者;(5)伴有严重感染、免疫系统疾病者;(6)哺乳或妊娠期患者;(7)心、肝、肾等功能不全者。

1.3 治疗方法

对照组患者给予表柔比星新辅助化疗,具体如下:化疗前给予格拉司琼注射液(四川宝鉴堂药业有限公司,国药准字H20057648,规格:3 mL:3 mg)3 mg,地塞米松片(佛山手心制药

有限公司,国药准字H44024501,规格:0.75 mg)0.75~3.00 mg,2次/d,进行抗敏治疗;表柔比星(北京协和药厂,国药准字H20143165,规格:10 mg)60 mg/m²,溶于0.9%的生理盐水100 mL中,缓慢静脉滴注,1次/周,3周为1个疗程,共治疗12周。研究组在对照组基础上联合消癌平注射液(国药准字Z20025868,南京圣和药业股份有限公司,规格:每支装2 mL(肌肉注射);20 mL(静脉注射))治疗,将60 mL消癌平注射液溶于5%葡萄糖注射液250 mL中,静脉滴注,1次/d,共治疗12周。

1.4 观察指标

(1)参考实体瘤疗效评价标准评判两组疗效,其中患侧乳房无可触及的肿块同时腋窝未触及肿大淋巴结为完全缓解;肿瘤最大径之和缩小≥30%,但未达到完全缓解,为部分缓解;肿瘤最大径之和缩小<30%,或有增大但<20%,为疾病稳定;肿瘤最大径之和增大≥20%,或化疗后出现新病灶、腋窝可触及淋巴结肿大为疾病进展。总有效率为完全缓解率与部分缓解率之和^[9]。(2)采用美国波士顿健康研究制定的健康调查简表(36-item short form, SF-36)^[10]评价两组治疗前、治疗12周后的生活质量, SF-36量表包括情感职能、生理功能、精神健康、躯体疼痛、生理职能、活力、总体健康及社会功能,每个维度各为100分,分数越高,生活质量越好。(3)抽取两组治疗前、治疗12周后的空腹静脉血6 mL,以3600 r/min的转速离心处理12 min,留取血清待测。采用美国BD公司生产的流式细胞仪检测Th17、CD4⁺CD25⁺Treg、Th17/Treg。采用酶联免疫吸附试验检测癌胚抗原(Carcinoembryonic antigen, CEA)、糖类抗原199(Carbohydrate antigen 199, CA199)、糖类抗原125(Carbohydrate antigen 125, CA125),严格遵守试剂盒说明书进行操作。(4)记录不良反应情况。

1.5 统计学方法

采用SPSS 25.0进行数据分析,以率(%)表示计数资料,采用卡方检验,用($\bar{x} \pm s$)表示计量资料,采用t检验,检验水准 $\alpha=0.05$ 。

2 结果

2.1 疗效对比

治疗12周后研究组的临床总有效率为91.11%(41/45),高于对照组的63.64%(28/44)($P<0.05$),具体如表1所示。

表1 两组疗效对比[例(%)]

Table 1 Comparison of curative effect between the two groups [n(%)]

Groups	Complete remission	Partial remission	Stable disease	Disease progression	Total effective rate
Control group(n=44)	11(25.00)	17(38.64)	10(22.73)	6(13.63)	28(63.64)
Study group(n=45)	16(35.56)	25(55.56)	2(4.44)	2(4.44)	41(91.11)
χ^2					9.639
P					0.002

2.2 两组生活质量评分对比

两组治疗前SF-36量表各维度评分对比无差异($P>0.05$),两组治疗12周后SF-36量表各维度评分升高,且研究组较对照组高($P<0.05$),具体如表2所示。

2.3 两组免疫功能指标对比

两组治疗前CD4⁺CD25⁺Treg、Th17、Th17/Treg对比无差异($P>0.05$),两组治疗12周后CD4⁺CD25⁺Treg、Th17/Treg均降低,且研究组较对照组低($P<0.05$),Th17升高,且研究组较对照组高($P<0.05$),具体如表3所示。

表 2 两组生活质量评分对比($\bar{x} \pm s$, 分)Table 2 Comparison of quality of life scores between the two groups($\bar{x} \pm s$, scores)

Groups	Time points	Physical pain	Physiological function	Vitality	Physiological functions	Mental health	Emotional function	Overall health	Social function
Control group (n=44)	Before treatment	45.39± 6.23	48.24± 6.42	54.88± 5.78	58.34± 6.54	52.73± 7.19	51.35± 6.24	52.53± 7.54	54.97± 8.63
	12 weeks after treatment	67.41± 6.18*	65.53± 7.37*	63.74± 5.46*	72.38± 6.23*	67.73± 6.14*	70.87± 7.39*	73.49± 6.67*	70.43± 7.62*
Study group (n=45)	Before treatment	55.94± 6.90	48.15± 6.01	54.58± 9.13	59.07± 7.96	52.38± 6.81	51.76± 6.31	52.97± 6.12	54.31± 6.27
	12 weeks after treatment	79.88± 7.34**	81.24± 6.25**	79.62± 10.04**	83.11± 7.16**	82.63± 8.92**	82.38± 7.27**	82.99± 8.14**	81.75± 7.31**

Note: compared with before treatment, * $P<0.05$; compared with control group, ** $P<0.05$.

表 3 两组免疫功能指标对比($\bar{x} \pm s$, %)Table 3 Comparison of immune function indexes between the two groups($\bar{x} \pm s$, %)

Groups	Time points	Th17	CD4 ⁺ CD25 ⁺ Treg	Th17/ Treg
Control group(n=44)	Before treatment	2.28± 0.25	19.14± 3.13	22.93± 2.87
	12 weeks after treatment	2.61± 0.21*	14.28± 3.52*	17.06± 2.34*
Study group(n=45)	Before treatment	2.31± 0.17	19.21± 3.97	23.09± 2.65
	12 weeks after treatment	4.18± 0.13**	10.32± 2.46**	12.51± 2.37**

Note: compared with before treatment, * $P<0.05$; compared with control group, ** $P<0.05$.

2.4 两组血清肿瘤标志物水平对比

两组治疗前 CEA、CA199、CA125 对比无差异($P>0.05$),两

组治疗 12 周后 CEA、CA199、CA125 均降低,且研究组较对照组低($P<0.05$),具体如表 4 所示。

表 4 两组血清肿瘤标志物水平对比($\bar{x} \pm s$)Table 4 Comparison of serum tumor markers between the two groups($\bar{x} \pm s$)

Groups	Time points	CEA(mg/L)	CA199(U/L)	CA125(U/L)
Control group(n=44)	Before treatment	25.69± 2.47	45.32± 3.51	152.39± 18.27
	12 weeks after treatment	17.25± 2.52*	32.41± 5.44*	105.44± 15.23*
Study group(n=45)	Before treatment	25.57± 2.51	45.37± 4.67	151.71± 17.04
	12 weeks after treatment	12.33± 2.48**	21.62± 3.45**	71.23± 14.36**

Note: compared with before treatment, * $P<0.05$; compared with control group, ** $P<0.05$.

2.5 不良反应发生率对比

对照组不良反应发生率为 31.82%(14/44),包括胃肠道异常 3 例、肝肾功能异常 4 例、骨髓抑制 2 例、恶心呕吐 5 例;研究组的不良反应发生率为 35.56%(16/45),包括胃肠道异常 3 例、肝肾功能异常 5 例、骨髓抑制 3 例、恶心呕吐 5 例;两组不良反应发生率对比未见统计学差异($\chi^2=0.139$, $P=0.709$)。

3 讨论

TNBC 作为乳腺癌的一种特殊亚型,具有以下生物学特征:(1)发病年龄早,易发生于初潮、怀孕年龄早、绝经前女性;(2)出现局部复发和远处转移的风险较早,且内脏转移率较高;(3)原发肿瘤体积较大,且淋巴结阳性率较非 TNBC 的比例高;(4)无病生存时间和总生存时间明显短于非 TNBC 者;(5)病理学类型几乎为浸润性导管癌;(6)对内分泌治疗和现有靶向治疗无效,治疗选择有限^[11-13]。国内外不少研究已证实 TNBC 由于

缺乏药物靶向受体,化疗是唯一推荐的可以改善预后的治疗措施^[14-16]。新辅助化疗指在实施局部治疗方法前所做的全身化疗,能够明显减少患者的肿瘤病灶、延缓病情的发展^[17]。表柔比星属于蒽醌类化合物,作为一种周期非特异性抗肿瘤药,可以嵌入肿瘤细胞的 DNA 链,进而阻碍细胞的转录过程及脱氧核糖核酸的形成,促进肿瘤细胞的凋亡^[18],同时,表柔比星还可通过抑制拓扑异构酶 II 的活性,发挥抑制肿瘤细胞增殖的作用^[19],但吴晓霞等人^[20]的研究结果显示,表柔比星应用于 TNBC 治疗中,总有效率为 43.5%,效果较差。消癌平注射液是经现代工艺制成的中成药,现有的不少研究表明^[21,22],消癌平注射液对多种恶性肿瘤均有抑制作用,临床已将其应用于宫颈癌、贲门癌中,并获得了较好的疗效。

本研究结果显示,研究组治疗后的临床总有效率较对照组高,可能是由于消癌平注射液中的生物碱可增加机体免疫功能,皂苷能抑制肿瘤新生血管形成,多糖可清除氧自由基^[23]。药

理研究也证实消癌平注射液可通过上调肿瘤坏死因子配体和受体家族、P53 基因、Caspase 家族基因等促凋亡基因的活性,并下调 BIK、Bcl2 等凋亡抑制基因的活性,最终发挥抗肿瘤的作用^[24]。本次研究结果还显示,研究组治疗 12 周后 CD4⁺CD25⁺Treg、Th17/ Treg 较对照组低,Th17 较对照组高,提示消癌平注射液具有改善机体免疫功能的作用,CD4⁺CD25⁺Treg 细胞特异性表达转录因子 Foxp3,可通过细胞间的直接接触或分泌细胞因子来抑制抗原特异性免疫应答,致使机体产生免疫耐受。Th17/ Treg 在正常人体中呈现一定的动态平衡,Th17/ Treg 失衡存在于多种免疫性疾病中^[25]。消癌平注射液可有效促使抗原及可溶性因素释放并抑制肿瘤生长,促使淋巴细胞亚群分泌,提高机体免疫调控能力^[26]。有研究报道消癌平注射液能有效激活 T 淋巴细胞、吞噬细胞及 NK 细胞,同时还可诱导胸腺淋巴细胞产生活性物质,调节机体细胞免疫^[27]。肿瘤标记物与肿瘤的生物行为密切相关,部分肿瘤标志物可反映治疗效果,CA125 是人体常见激素类型,在卵巢癌和子宫内膜癌患者中有较高的检出率,在乳腺癌患者中同样也存在高表达^[28]。CA199 是一种类黏蛋白的糖蛋白,其量变可提示肿瘤的性质^[29]。CEA 是一种具有人类胚胎抗原特性的酸性糖蛋白,在中晚期乳腺癌患者中表达上升^[30]。本次研究结果显示,研究组治疗 12 周后 CEA、CA199、CA125 低于对照组,表明消癌平注射液联合表柔比星新辅助化疗治疗 TNBC,可改善血清肿瘤标志物水平。此外,研究组患者的 SF-36 量表各维度评分高于对照组,两组不良反应发生率对比未见统计学差异,进一步证实了消癌平注射液联合表柔比星新辅助化疗治疗的效果更佳,且不增加不良反应,对提高患者的生活质量有利。本研究尚存在样本量偏小、时间限制未能考察患者远期生存情况等不足,有待进一步的深入研究。

综上所述,消癌平注射液联合表柔比星新辅助化疗治疗 TNBC,具有确切的治疗效果,可有效阻止疾病进展,改善患者免疫功能、生活质量,降低血清肿瘤标志物水平。

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