·论著·

吉西他滨联合顺铂治疗晚期triple-negative乳腺癌效果及对肿瘤标志物、癌因性疲乏的影响

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【摘要】**目的** 探讨吉西他滨联合顺铂治疗晚期triple-negative乳腺癌患者的临床疗效及对肿瘤标志物、癌因性疲乏的影响。**方法** 按随机数字表法，将2017年5月至2019年5月某院收治的晚期triple-negative乳腺癌患者117例分为观察组(n=59)与对照组(n=58)，观察组采用吉西他滨+顺铂治疗，对照组采用吉西他滨+卡铂治疗。比较两组治疗效果，分析治疗前、治疗6周后肿瘤标志物与癌因性疲乏评分差异。**结果** 观察组总缓解率为67.79%，明显高于对照组51.72%(*P*<0.05)。治疗6周后，两组血清肿瘤标志物CA125、CA153、CEA、TPS较治疗前均下降，且观察组明显低于对照组(*P*<0.05)；两组癌因性疲乏评分较治疗前均下降，且观察组明显低于对照组(*P*<0.05)。**结论** 对于晚期triple-negative乳腺癌患者初次用吉西他滨联合顺铂放化疗治疗，其效果显著，可以降低CA125、CA153、CEA、TPS的含量，有效减轻癌因性疲乏。

【关键词】triple-negative乳腺癌，晚期；吉西他滨；顺铂；肿瘤标志物；癌因性疲乏；疗效
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Effect of Gemcitabine Combined with Cisplatin in the Treatment of Advanced Triple-negative Breast Cancer and Its Effects on Tumor Markers and Cancer-related Fatigue

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Abstract: ***Objective*** To investigate the clinical efficacy of gemcitabine combined with cisplatin in the treatment of patients with advanced triple-negative breast cancer and its effect on tumor markers and cancer-related fatigue. ***Methods*** According to the random number table method, 117 patients with advanced triple-negative breast cancer admitted to a hospital from May 2017 to May 2019 were divided into an observation group (n=59) and a control group (n=58). The patients were treated with gemcitabine + cisplatin, and the control group was treated with gemcitabine + carboplatin. The therapeutic effects of the two groups were compared, and the differences in tumor markers and cancer-related fatigue scores before and after 6 weeks of treatment were analyzed. ***Results*** The total remission rate of the observation group was 67.79%, which was significantly higher than that of the control group, 51.72% (*P*<0.05). After 6 weeks of treatment, the serum tumor markers CA125, CA153, CEA and TPS in the two groups were decreased compared with those before treatment, and the observation group was significantly lower than the control group (*P*<0.05); the cancer-related fatigue scores in both groups were decreased compared with those before treatment , and the observation group was significantly lower than the control group (*P*<0.05). ***Conclusion*** Gemcitabine combined with cisplatin chemoradiotherapy for the first time in patients with advanced triple-negative breast cancer has a significant effect, which can reduce the contents of CA125, CA153, CEA and TPS, and effectively relieve cancer-related fatigue.

Keywords: Triple-negative Breast Cancer, Advanced Stage; Gemcitabine; Cisplatin; Tumor Markers; Cancer-related Fatigue; Efficacy

triple-negative乳腺癌(triple-negative breast cancer，TNBC)是指患者雌激素受体(ER)、孕激素受体(PR)、原癌基因(HER-2)均为阴性，即三阴性乳腺癌。临床治疗乳腺癌的常用手段有：手术切除、靶向治疗、内分泌治疗、放化疗等。因triple-negative乳腺癌ER、PR与HER-2均为阴性，内分泌治疗与靶向治疗对此类患者无效[1]，放化疗是治疗该类患者的主要方法[2]。肿瘤标志物可以在癌症患者血液、尿液、粪便、肿瘤及其他组织中出现的较正常人高的特殊物质，如CA125、CA153、CEA。此外，在乳腺癌患者中TPS也呈高表达[3]。有关学者认为，癌因性疲乏是影响乳腺癌患者生活质量的最直接因素，其疲劳程度会对患者生活质量造成严重影响[4]。吉西他滨联合顺铂在恶性肿瘤治疗中得到了广泛的认可与应用，效果较好[5]。但目前关于吉西他滨联合顺铂对晚期triple-negative乳腺癌肿瘤标志物及癌因性疲乏的影响仍需进一步做深入研究。本研究旨在观察吉西他滨联合顺铂治疗晚期triple-negative乳腺癌的临床疗效，并分析其对肿瘤标志物及癌因性疲乏的影响，以期为乳腺癌的临床治疗提供一定的参考价值。

1 资料与方法

1.1 一般资料 选取某院2017年5月至2019年5月收治入院的晚期triple-negative乳腺癌患者117例，按随机数字表法将其分为观察组(n=59)与对照组(n=58)。观察组年龄41~62岁，平均年龄(51.4±4.9)岁；分化程度：低分化15例，中分化21例，高分化23例；肿瘤分期：Ⅲ期35例，Ⅳ期24例；病理分型：腺癌13例，鳞癌18例，鳞腺癌28例；转移情况：脑4例，肝11例，淋巴结19例，肺部25例。月经状况：绝经前40例，绝经后19例。对照组年龄40~62岁，平均年龄(50.4±4.3)岁；分化程度：低分化14例，中分化22例，高分化22例；肿瘤分期：Ⅲ期34例，Ⅳ期24例；病理分型：腺癌14例，鳞癌15例，鳞腺癌29例；转移情况：脑6例，肝12例，淋巴结17例，肺部23例。月经状况：绝经前42例，绝经后16例。两组临床资料差异无显著(*P*>0.05)，有对比性。

纳入标准：病理确诊为triple-negative乳腺癌；临床分期：Ⅲ~Ⅳ期；预计生存时间大于3个月；初次行放化疗；患者临床资料完整者；患者及家属自愿签署知情同意书。排除标准：合并有其他恶性肿瘤者；处于妊娠或哺乳期的妇女；有乳腺癌家庭史者；有精神障碍者；有放化疗药物过敏史者；对放化疗不能耐受，中途退出者；临床资料不完整者。

1.2 方法

1.2.1 治疗方法 观察组采用吉西他滨+顺铂治疗。吉西他滨(规

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格：1.0g/0.2g；生产单位：江苏豪森药业股份有限公司；批准文号：国药准字H20030105)1000mg/m^2，d1、d8、d15静脉滴注。顺铂(规格：10mg/支，生产单位：齐鲁制药有限公司，批准文号：国药准字H37021358)25mg/m^2，d1~d3静脉滴注，21d为1个疗程，治疗2个疗程。对照组采用吉西他滨+卡铂治疗。吉西他滨用法及用量同观察组。卡铂(规格：0.1 g×6支，生产单位：齐鲁制药有限公司，批准文号：H10920028)400mg/m^2，静脉滴注d1，21d为1个疗程，治疗2个疗程。

1.2.2 指标检测方法 所有患者入院后于治疗前、治疗6周后空腹抽取患者肘静脉血3mL，室温静置30min，以3000r/min离心10min，分离血清后置于管内-80℃冷存待检。应用免疫检测仪及配套试剂对血清肿瘤标记物[链糖抗原(CA125)、链糖抗原(CA153)、癌胚抗原(CEA)、组织多肽特异性抗原(TPS)]水平采用电化学发光法进行检测。

1.3 疗效判定标准[6] 采用实体瘤疗效评价标准(response evaluation criteria solid tumors，RECIST)。完全缓解：所有目标病灶全部消失；部分缓解：患者基线病灶长径总和缩小30%及以上；稳定：患者基线病灶长径总和增大且大于20%而小于30%；疾病进展：患者肿瘤体积增大20%及以上或是出现了新病灶。*总有效率=(完全缓解+部分缓解)/总例数×100.0%*。

1.4 观察指标

1.4.1 肿瘤标志物 比较治疗前、治疗6后肿瘤标志物CA125、CA153、CEA、TPS的水平变化。

1.4.2 癌因性疲乏评分 采用中文版Piper疲乏修订量表(piper fatigue scale，PFS)。该量表包含4个维度：认知疲乏、情感疲乏、躯体疲乏、行为疲乏，共22个条目。总分0~10分，得分越低，说明患者的疲乏程度越轻。该量表在临床乳腺癌患者中得到了大量的实验验证，且已被翻译成多种版本，具有良好的信效度。

1.5 统计学方法 对本研究数据采用SPSS 19.0进行统计分析，符合正态分布的计量资料采用($\bar{x}\pm s$)表示，组间行t检验。计数资料采用例数、百分比(%)表示，组间行χ^2检验。*P*<0.05差异有统计学意义。

2 结 果

2.1 两组临床疗效比较 观察组总缓解率为67.79%，明显高于对照组51.72%(*P*<0.05)，见表1。

表1 两组临床疗效比较

组别	例数	完全缓解	部分缓解	稳定	疾病进展	总缓解率
观察组	59	21	19	18	1	67.79(10/59)
对照组	58	16	14	18	10	51.72(30/38)
χ^2值						8.789
*P*值						0.032

2.2 治疗前后两组肿瘤标志物水平变化 两组治疗前血清CA125、CA153、CEA、TPS比较无差异(*P*>0.05)；治疗6周后，两组4项肿瘤标志物指标水平较治疗前均下降，且观察组明显低于对照组(*P*<0.05)，见表2。

2.3 治疗前后两组癌因性疲乏状况比较 两组治疗前认知、躯体、情感、行为疲乏评分比较无差异(*P*>0.05)；治疗6周后，两组4项疲乏评分较治疗前均下降，且观察组明显低于对照组(*P*<0.05)，见表3。

表2 治疗前后两组肿瘤标志物水平变化

组别		CA125(IU/mL)	CA153(IU/mL)	CEA(ng/mL)	TPS(IU/mL)
观察组(n=59)	治疗前	73.36±6.12	66.54±6.62	10.10±1.06	412.54±106.14
	治疗6周后	26.84±3.63[a]	28.36±3.24[a]	5.10±0.54[a]	218.46±52.49[a]
	t值	50.218	39.790	32.284	12.590
	*P*值	0.000	0.000	0.000	0.000
对照组(n=59)	治疗前	72.15±5.60	67.14±5.61	10.32±1.08	411.04±104.12
	治疗6周后	41.31±4.53[ab]	47.23±4.13[ab]	7.48±0.81[ab]	337.23±53.35[ab]
	t值	32.608	21.766	16.021	7.805
	*P*值	0.000	0.000	0.000	0.000
	t_1值	19.083	27.522	18.730	9.785
	P_1值	0.000	0.000	0.000	0.000

注：a与治疗前比较，*P*<0.05；b与观察组比较，*P*<0.05；t_1、P_1分别为治疗后两组4项肿瘤标志物的比较；CA125：糖类抗原125；CA153：糖类抗原153；CEA：癌胚抗原；TPS：组织多肽特异性抗原。

表3 治疗前后两组癌因性疲乏状况比较

组别		认知疲乏	躯体疲乏	情感疲乏	行为疲乏
观察组(n=59)	治疗前	4.1±1.0	5.9±0.9	5.8±1.0	5.2±0.7
	治疗6周后	3.5±0.9[a]	4.6±1.0[a]	4.5±1.0[a]	4.4±0.7[a]
	t值	3.426	7.422	7.061	6.207
	*P*值	0.001	0.000	0.000	0.000
对照组(n=59)	治疗前	4.2±1.1	5.8±1.0	5.9±0.9	5.3±0.6
	治疗6周后	3.8±0.6[ab]	5.1±0.9[ab]	5.0±1.1[ab]	4.9±0.6
	t值	2.143	3.963	4.823	3.590
	*P*值	0.034	0.000	0.000	0.000
	t_1值	2.118	2.841	2.573	4.145
	P_1值	0.036	0.005	0.011	0.000

注：a与治疗前比较，*P*<0.05；b与观察组比较，*P*<0.05；t_1、P_1分别为治疗后两组4个维度的比较

3 讨 论

国家癌症中心发布的《2015年恶性肿瘤发病率与死亡率报告》[7]：乳腺癌占恶性肿瘤发病率的第5位(女性恶性肿瘤的首位)，占恶性肿瘤死亡率的第6位。发病率呈年轻化趋势逐年增加，以北上广一线城市的女性发病率最高。triple-negative乳腺癌是一种在分子分型、病理及临床特征均较特殊的一类，具有高侵袭性、高复发性、预后极差的特点。临床治疗中对蒽环类药物敏感度不高，且因自身特性限制了内分泌及靶向治疗，临床治疗难度很大，可用药物更是少之又少。因此，寻找有针对性的有效的化疗药物对triple-negative乳腺癌的治疗具有重要意义。triple-negative乳腺癌BRCA1基因存在突变，且BRCA1基因与DNA断裂、修复有关系，因此对抑制DNA修复的化疗药物敏感。铂类药物因与患者体内DNA结合，抑制了DNA的复制与转录，提高患者临床疗效。Hill等[8]报道，顺铂单药治疗晚期triple-negative乳腺癌的总有效率为20%~50%。吉西他滨主要抑制DNA修复，还通过抑制核糖核酸还原酶，使三磷酸脱氧核苷产生量减少，尤其是脱氧三磷酸胞苷减少，最终导致细胞凋亡。Wang等[9]报道，单纯使用吉西他滨治疗晚期triple-negative乳腺癌的总有效率为25%~38%。二者具有协同作用。Wang等[10]报道，顺铂+吉西他滨在治疗晚期triple-negative乳腺癌的总有效率为22%~63%。

本研究结果显示：观察组总缓解率67.8%，中位肿瘤进展时间9个月。解国清等[11]报道，顺铂+吉西他滨治疗晚期triple-negative乳腺癌的总缓解率为65.8%，中位肿瘤进展时间5个月，与本研究结果相差不大。观察组CA125、CA153、CEA、TPS水平均比对照组低，这提示了顺铂与吉西他滨对乳腺癌的肿瘤生长起到抑制作用。观察组癌因性疲乏与对照组相比明显较低，这提示顺铂与吉西他滨改善了该类患者的生活质量，患者疲乏程度减轻。与黎胤谋等[12]报道相一致。

综上所述，吉西他滨联合顺铂对于初治的晚期triple-negative乳腺癌患者疗效显著，可以降低CA125、CA153、CEA、TPS的含量，有效减轻癌因性疲乏。本研究由于样本量小，来源单一，且癌因性疲乏评分主要通过患者的主观感受进行描述，导致本研究不能完全的真实的反映实验结果，日后需进一步进行多中心大样本研究，为临床治疗提供依据。

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（上接第 54 页）

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