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化疗对乳腺癌患者激素水平及月经状态的影响 *

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摘要 目的:讨论乳腺癌患者术后辅助化疗对患者激素水平及月经状况的影响。**方法:**收集我院2014年1月-2015年8月初诊绝经前乳腺癌患者78例,绝经后乳腺癌患者50例,检测化疗前及化疗结束后的雌二醇(E2)、黄体生成素(LH)、卵泡刺激素(FSH)水平,随访绝经前乳腺癌患者化疗期间及化疗后月经变化情况。**结果:**绝经前乳腺癌患者化疗后E2水平明显下降,FSH、LH水平明显升高,差异具有统计学意义($P<0.05$),绝经后乳腺癌患者化疗后E2水平无明显变化($P>0.05$),FSH、LH水平均下降,差异具有统计学意义($P<0.05$)。绝经前乳腺癌患者三个不同年龄段化疗后E2水平降低,而FSH、LH水平升高,差异具有统计学意义($P<0.05$),但三个不同年龄段患者化疗前后性激素水平组间比较均无统计学差异($P>0.05$)。绝经前乳腺癌患者三个不同年龄段化疗后闭经率比较差异具有统计学意义($P<0.05$)。绝经前乳腺癌患者化疗后闭经患者E2水平明显低于未闭经患者,FSH、LH水平明显高于未闭经患者,差异具有统计学意义($P<0.05$)。**结论:**化疗可影响乳腺癌患者E2、FSH、LH水平,导致患者闭经,闭经情况与患者年龄有关。

关键词:乳腺癌;化疗;雌二醇;黄体生成素;卵泡刺激素;月经

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Effect of Chemotherapy on Hormone Levels and Menstrual Status in Patients with Breast Cancer*

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ABSTRACT Objective: To study the effect of adjuvant chemotherapy on hormone levels and menstrual status in patients with breast cancer. **Methods:** A total of 78 premenopausal women and 50 postmenopausal women, who were diagnosed as breast cancer in Second People's Hospital of Yibin from January 2014 to August 2015, were collected. The levels of estradiol (E2), luteinizing hormone (LH), follicle-stimulating hormone (FSH) of all the patients were detected before and after chemotherapy. The menstrual changes of premenopausal patients with breast cancer during chemotherapy and after chemotherapy were followed up. **Results:** After chemotherapy, the levels of E2 were significantly decreased in premenopausal breast cancer patients, while the levels of FSH and LH were significantly increased, the differences were statistically significant ($P<0.05$). There was no significant change in the levels of E2 after chemotherapy in postmenopausal breast cancer patients ($P>0.05$), but the levels of FSH and LH were significantly decreased, the differences were statistically significant ($P<0.05$). After chemotherapy, the levels of E2 were decreased and the levels of FSH and LH were increased in three different ages of premenopausal breast cancer patients, the differences were statistically significant ($P<0.05$); but there was no significant difference in sex hormone levels among them before and after chemotherapy ($P>0.05$). There was significant difference in amenorrhea rate after chemotherapy among the three different ages of premenopausal breast cancer patients ($P<0.05$). The levels of E2 in premenopausal patients with amenorrhea after chemotherapy were significantly lower than that in patients without amenorrhea, and the levels of FSH and LH were significantly higher than those without amenorrhea, and the difference was statistically significant ($P<0.05$). **Conclusion:** Chemotherapy can affect the levels of E2, FSH and LH in the patients with breast cancer, and can lead to amenorrhea, and amenorrhea is related to the age of the patients.

Key words: Breast cancer; Chemotherapy; Estradiol; Luteinizing hormone; Follicle-stimulating hormone; Menstruation

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前言

乳腺癌是发生在乳腺腺上皮组织的恶性肿瘤,其发病率呈现逐年递增趋势,在女性恶性肿瘤疾病中较为常见,且患者趋

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于年轻化,对我国女性的生命健康构成巨大威胁,探究有效且合理的治疗方案对具有重要的临床意义^[1-3]。早在上个世纪,已有报道显示乳腺癌为全身性疾病,主要治疗方式是局部治疗和全身治疗,其中全身治疗是以化疗为主,并且受到广泛的关注^[4-6]。辅助化疗延长了年轻乳腺癌患者的无病生存期和总生存期^[7],与此同时,来曲唑、阿那曲唑、依西美坦等第三代芳香化酶抑制剂应用到临床研究,结果显示:对于绝经后激素受体阳性乳腺癌患者,第三代芳香化酶抑制剂疗效优于三苯氧胺^[8,9]。但是,化疗会导致20%-70%的绝经前乳腺癌患者发生闭经,化疗导致闭经的发生与化疗药物的种类、剂量、周期及患者年龄有关^[10,11]。如果我们将化疗导致闭经误认为是绝经,将会导致第三代芳香化酶抑制剂的误用,正因为如此,美国综合肿瘤网络中心(national Comprehensive Cancer Network, NCCN)指南推荐化疗导致闭经患者需检测雌二醇(estradiol, E2)、卵泡刺激素(follicle stimulating hormone, FSH)水平以确认其是否绝经^[12]。本研究期望讨论化疗对乳腺癌激素水平及月经状态的影响,为第三代芳香化酶抑制剂的选择提供理论依据,现报道如下。

1 资料与方法

1.1 选择对象

收集我院2014年1月-2015年8月初诊绝经前乳腺癌患者78例,年龄28-51岁,平均 (42.8 ± 5.6) 岁,其中 ≤ 40 岁19例,40-45岁25例, ≥ 45 岁34例。绝经后乳腺癌患者50例,年龄47-68岁,平均 (57.3 ± 4.7) 岁,纳入标准:(1)所有患者的诊断均经病理证实;(2)均完成TEC/TAC方案化疗6周期;(3)均顺利完成随访;(4)患者及其家属对本研究知情同意,并签署知情同意书。排除标准:(1)黄疸患者、溶血患者、类风湿患者;(2)卵巢手术者;(3)放疗药物过敏者;(4)合并影响性激素分泌疾病者,如腺垂体肿瘤、卵巢肿瘤、甲亢等;(5)合并有其他恶性肿瘤者。本研究经医院伦理委员会审核通过。

1.2 化疗方案

TEC:多西他赛(江苏恒瑞医药股份有限公司,国药准字:H20020543,规格:0.5 mL: 20 mg)75mg/m²,表柔比星(海正辉瑞

制药有限公司,国药准字:H19990280,规格:10mg)75 mg/m²,环磷酰胺(江苏盛迪医药有限公司,国药准字:H32020857,规格:0.2g)500 mg/m²;TAC:多西他赛 75 mg/m²,多柔比星(山西普德药业有限公司,国药准字:H14023143,规格:10 mg)50 mg/m²,环磷酰胺 500 mg/m²,所有药物第1d经PICC置管输入,21d为1个周期,应用多西他赛前常规予以地塞米松预防过敏。

1.3 观察指标

绝经后乳腺癌患者在化疗前1d及化疗后第7d检测血清E2、FSH、黄体生成素(luteinizing hormone, LH)水平;绝经前乳腺癌患者在化疗前、月经滤泡期(月经周期5-14d)检测血清E2、FSH、LH水平,其中化疗导致月经停止患者于化疗后第7d检测血清E2、FSH、LH水平,均由雅培化学发光法检测。每次入院时记录月经状态,并通过电话询问、门诊复查等方式对化疗后所有患者进行为期2年以上的随访时间。化疗致闭经(chemotherapy-induced amenorrhea, CIA)是指化疗期间及化疗后1年内出现停经,且持续6个月以上者。闭经率=化疗致闭经患者例数/绝经前乳腺癌患者例数 $\times 100\%$ 。其中闭经后12个月之内月经恢复则定义为月经复潮(menstruation recovery, MR)。

1.4 统计学方法

所有数据使用SPSS20.0分析软件分析,激素水平等计量资料以 $(\bar{x} \pm s)$ 表示,用t检验或重复测量方差分析比较;闭经率行 χ^2 检验分析,所有P值来源于双侧检验, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 化疗前后性激素水平比较

绝经前乳腺癌患者经化疗后E2水平明显下降,而FSH、LH水平则明显升高,差异具有统计学意义($P < 0.05$),绝经后乳腺癌患者化疗后E2水平无明显变化,FSH、LH水平均下降,差异具有统计学意义($P < 0.05$)。见表1。

表1 化疗前后性激素水平比较($\bar{x} \pm s$)

Table 1 Comparison of sex hormone levels before and after chemotherapy($\bar{x} \pm s$)

Groups	Times	E2(pmol/L)	FSH(mIU/mL)	LH(mIU/mL)
Premenopausal breast cancer patients(n=78)	Before chemotherapy	125.77 $\pm$ 105.16	11.91 $\pm$ 13.93	8.91 $\pm$ 9.10
	After chemotherapy	25.74 $\pm$ 20.32	84.43 $\pm$ 33.40	44.10 $\pm$ 19.35
	t	8.248	17.698	14.534
	P	0.000	0.000	0.000
Postmenopausal breast cancer patients(n=50)	Before chemotherapy	15.69 $\pm$ 8.59	79.81 $\pm$ 29.18	30.08 $\pm$ 11.65
	After chemotherapy	17.71 $\pm$ 9.97	72.22 $\pm$ 20.33	28.04 $\pm$ 9.29
	t	1.285	2.648	2.356
	P	0.202	0.034	0.042

2.2 绝经前乳腺癌患者不同年龄段性激素水平比较

三个不同年龄段患者化疗后E2水平降低,而FSH、LH水平升高,差异具有统计学意义($P < 0.05$),但三个不同年龄段患

者化疗前后性激素水平组间比较均无统计学差异($P > 0.05$)。见表2。

表 2 绝经前乳腺癌患者不同年龄段性激素水平比较($\bar{x} \pm s$)Table 2 Comparison of sex hormone levels in premenopausal breast cancer patients at different ages($\bar{x} \pm s$)

Ages (years)	n	E2(pmol/L)		FSH(mIU/mL)		LH(mIU/mL)	
		Before chemotherapy	After chemotherapy	Before chemotherapy	After chemotherapy	Before chemotherapy	After chemotherapy
≤ 40	19	102.42± 21.97	33.79± 13.93*	9.77± 2.76	82.83± 26.67*	8.26± 1.52	46.46± 9.95*
40-45	25	112.76± 25.32	29.36± 12.70*	10.43± 1.94	78.58± 18.02*	8.76± 1.80	41.74± 8.59*
≥ 45	34	115.05± 29.15	25.58± 9.97*	11.87± 1.40	85.83± 19.35*	8.95± 2.18	44.53± 8.74*
F		1.429	1.099	0.932	1.464	0.975	1.686
P		0.163	0.278	0.357	0.149	0.335	0.099

Note: Compared with before chemotherapy, *P<0.05.

2.3 绝经前乳腺癌患者不同年龄段化疗后闭经情况

同年龄段患者化疗后闭经率比较差异具有统计学意义(P<0.

绝经前乳腺癌患者化疗后总体闭经率为 58.97%，三个不 05)。见表 3。

表 3 绝经前乳腺癌患者不同年龄段化疗后闭经情况[n(%)]

Table 3 Amenorrhea after chemotherapy in premenopausal breast cancer patients at different ages[n(%)]

Ages (years)	n	Amenorrhea cases	Amenorrhea rate
≤ 40	19	6	31.58
40-45	25	15	60.00
≥ 45	34	25	73.53
χ^2			8.882
P			0.012

2.4 绝经前乳腺癌患者化疗后闭经与未闭经患者性激素水平比较

比,闭经患者 E2 水平明显较低,FSH、LH 水平明显较高,差异具有统计学意义(P<0.05)。见表 4。

绝经前乳腺癌患者,经化疗后闭经患者与未闭经患者相

表 4 绝经前乳腺癌患者化疗后闭经与未闭经患者性激素水平比较($\bar{x} \pm s$)

Table 4 Comparison of sex hormone levels between premenopausal breast cancer patients with amenorrhea and without amenorrhea after chemotherapy

Menstrual state	n	E2(pmol/L)	FSH(mIU/mL)	LH(mIU/mL)
Without amenorrhea	32	43.78± 19.45	71.58± 36.52	37.99± 18.31
Amenorrhea	46	13.20± 7.35	93.37± 28.12	48.36± 19.10
t		9.733	-2.975	-2.399
P		0.000	0.006	0.018

3 讨论

现有研究报道,乳腺癌已成为女性癌症死亡的第二大"杀手",据估计美国今年将有 255180 例新发乳腺癌患者,约 40610 名妇女死于乳腺癌^[13-15]。辅助化疗延长了乳腺癌患者的无病生存期和总生存期,但也会引起长期的副作用,例如卵巢功能障碍,包括暂时或永久性的闭经、不孕、过早绝经等,甚至会增加心血管功能障碍发生的风险^[16-18]。在年轻女性中,经辅助化疗诱导闭经的发生率从 21%到 71%,在 40 岁以上的女性中,发生率从 49%到 100%^[19]。本研究中总体闭经率为 58.97%,40 岁以下患者闭经率为 31.58%,40-45 岁患者闭经率为 60.00%,大于 45 岁患者闭经率为 73.53%,三个不同年龄段患者化疗致闭经率比较差异具有统计学意义(P<0.05),与既往研究^[20]结果相似,可能的原因是辅助化疗可降低体内卵泡数量、导致黄体功能丧失,严重影响卵巢功能,相关研究发现,环磷酰胺可导致

大卵泡丢失,并可对机体的垂体在反馈机制促进生成的小卵泡造成破坏,导致小卵泡的数量减少,长时间作用可导致卵巢功能衰竭,进而发生闭经^[21-23]。

FSH、LH、E2 等水平常用于评估癌症患者卵巢功能,绝经前女性 E2 直接由卵泡的颗粒细胞产生,对下丘脑-垂体-卵巢轴有负反馈作用,是卵巢功能的直接指标^[24,25]。化疗使卵巢皮质纤维化、卵泡闭锁,雌孕激素分泌减少,雌激素反馈性作用于下丘脑,促进促性腺激素释放激素(Gonadotropin releasing hormone, GnRH)分泌, GnRH 又进一步促进垂体 LH 和 FSH 分泌,从而出现化疗会导致绝经前患者雌激素水平下降,促性腺激素水平上升^[26,27]。本研究中绝经前乳腺癌患者经化疗后 E2 水平明显下降,而 FSH、LH 水平则明显升高(P<0.05),与既往研究结果类似。绝经后女性由于卵巢功能的自然萎缩,雌激素不再由卵巢产生,而主要是依赖于 C19 雄激素前体在局部转化, C19 雄激素主要来源于肾上腺皮质,在羟基类固醇脱氢酶的作用

下,雄烯二醇和脱氢表雄酮在性腺外组织中分别转化为睾酮和雄烯二酮,然后在芳香化酶的介导下分别转化为 E1 和 E2^[28]。本研究中化疗前后绝经后乳腺癌患者 E2 水平无明显变化,说明化疗可能对绝经后妇女 E2 的产生无明显影响,而化疗后 FSH、LH 均下降,化疗是否直接作用于下丘脑-垂体导致促性腺激素水平下降,还需更多研究证实。

本研究中绝经前乳腺癌患者化疗后闭经患者 E2 水平较未闭经患者明显较低,FSH、LH 水平明显较高($P<0.05$),说明激素水平可用于评估卵巢功能受损程度,但是不同年龄段激素水平变化比较无统计学差异($P>0.05$),不同年龄段患者化疗后闭经率比较差异具有统计学意义($P<0.05$),化疗导致的临床"闭经"与内分泌学"绝经"约有一定的分离现象。越来越多的乳腺癌患者在诊断时处于绝经前或围绝经期,她们的月经会因为化疗而停止,如若未在有效的卵巢抑制下使用芳香化酶抑制剂(aromatase inhibitors, AIs),可能导致 AIs 引起卵巢过度刺激,增加意外妊娠,升高 E2 水平^[29,30]。乳腺癌患者化疗后更年期的定义和生理变化是错综复杂的,因此准确评估卵巢功能和绝经状态对内分泌治疗的选择至关重要。

综上所述,化疗可使绝经前乳腺癌患者 E2 水平降低,FSH、LH 水平升高,且对绝经前乳腺癌患者闭经的影响与年龄相关,在临床治疗时应根据患者的具体情况来选择合适的化疗方案。

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