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# 药学干预对乳腺癌患者辅助化疗期间恶心呕吐和生活质量影响的研究\*

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**摘要 目的:**探讨药学干预对乳腺癌患者辅助化疗期间恶心呕吐和生活质量的影响。**方法:**采用前瞻性队列研究,共入组87例乳腺癌术后患者。在接受辅助化疗前随机分为干预组(n=44)和对照组(n=43),干预组患者在接受化疗和常规支持治疗的同时,针对化疗引起的恶心呕吐由临床药师对患者进行咨询并指导用药,优化对症治疗方案,对照组仅接受化疗和常规支持治疗。比较两组患者对止吐药物的完全反应率、恶心严重程度、呕吐频次和生活质量。**结果:**化疗的前3个周期两组对止吐药物的完全缓解率分别为37.2%和63.6%,46.5%和75.0%,44.2%和72.7%,干预组完全缓解率明显高于对照组( $P=0.014$ ,  $P=0.006$ ,  $P=0.007$ )。干预组的急性和迟发性恶心较对照组轻( $P=0.023$ ,  $P=0.045$ ),急性和迟发性呕吐频率较对照组明显减少( $P=0.006$ ,  $P=0.034$ )。生活质量测评显示干预组患者的总健康状况较对照组升高( $P=0.028$ ),恶心、呕吐和食欲丧失的症状评分较对照组降低( $P=0.025$ ,  $P=0.045$ )。**结论:**临床药师对乳腺癌患者辅助化疗期间进行药学干预可明显减轻患者恶心、呕吐的副反应,并可改善生活质量。临床药师参与乳腺癌患者辅助化疗期间的对症治疗值得在临床广泛推广。

**关键词:**药学干预;乳腺癌;化疗;恶心;呕吐;生活质量

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## Effects of Pharmaceutical Intervention on Nausea and Vomiting as well as Quality of Life in Breast Cancer Patients Undergoing Adjuvant Chemotherapy\*

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**ABSTRACT Objective:** To investigate the effects of pharmaceutical intervention on nausea and vomiting as well as quality of life in breast cancer patients undergoing adjuvant chemotherapy. **Methods:** A total of 87 women surgically treated for breast cancer were randomly divided into two either intervention (n=44) or control group (n=43) before adjuvant chemotherapy. The intervention group received pharmaceutical intervention and routine health care during adjuvant chemotherapy, whereas the control group only received routine health care. Response rate to antiemetics, severity of nausea, frequency of vomiting and quality of life were compared between the two groups. **Results:** The complete response rates to antiemetic drugs in the two groups during the first three cycles of chemotherapy were 37.2% and 63.6%, 46.5% and 75.0%, 44.2% and 72.7%. Compared with the control group, patients in the intervention group acquired significantly higher complete response rate ( $P=0.014$ ,  $P=0.006$ ,  $P=0.007$ ). The symptom of acute and delayed nausea in the intervention group were less severe than that in the control group ( $P=0.023$ ,  $P=0.045$ ). Moreover, the frequency of acute and delayed vomiting were significantly reduced compared with the control group ( $P=0.006$ ,  $P=0.034$ ). Quality of life evaluation showed the global health status of the patients in the intervention group was better than in the control group ( $P=0.023$ ), while the symptom scores in terms of nausea, vomiting and loss of appetite were reduced ( $P=0.034$ ) as compared with the control group. **Conclusion:** Pharmaceutical intervention during adjuvant chemotherapy for breast cancer patients can not only reduce the side effects of nausea and vomiting but also improve the quality of life.

**Key words:** Pharmaceutical intervention; Breast cancer; Chemotherapy; Nausea; Vomiting; Quality of life

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### 前言

乳腺癌是女性最常见的恶性肿瘤,其常见的治疗模式包括手术、化疗、放疗、内分泌和分子靶向治疗等<sup>[1]</sup>。然而,所有抗肿瘤

治疗不可避免的会带来诸多毒副反应,因此探索有效的对症支持治疗方案以预防或减轻这些毒副反应显得刻不容缓。尽管有关化疗引发毒副反应的处理已经有可遵循的国际指南和推荐,但由于医师对其执行程度不同、患者依从性不一等种种因

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素,使得这些对症处理措施与患者实际需求之间还存在一定差距,因此需要探索可行途径对此加以转变和改善<sup>[2]</sup>。药学干预或护理是临床药师为增强疗效和改善生活质量而对医师提供的用药方面的指导和建议。研究显示,合理开展药学干预有助于规范临床医师合理用药,改善患者的临床症状和生活质量。肿瘤患者的药学干预在国外开展的比较早,大多采用前瞻性队列研究或随机对照研究实施,取得了较好的效果,但在国内这方面工作起步较晚,相关报道并不多见。本研究以医院推行的药师指导临床用药为背景,设计了前瞻性队列研究,重点探讨了临床药师对乳腺癌辅助化疗患者进行药学干预对消化道毒副反应和生活质量的影响,以探索临床药师干预在肿瘤多学科治疗中所发挥的作用,为进一步规范临床医师的用药、改善肿瘤患者生存预后提供借鉴方法。

## 1 材料与方法

### 1.1 患者入组

采用前瞻性队列研究,选取 2011 年 6 月至 2012 年 6 月经病理明确诊断为乳腺癌并接受了手术治疗(含保乳手术、改良根治术、扩大根治术),需要进行辅助化疗的患者(联合或不联合靶向治疗)。患者应满 18 岁,具有一定的阅读和沟通能力,能够完成问卷调查。患者入组前均签署知情同意书。最终共 87 例患者入组。

### 1.2 药学干预

两组患者均根据乳腺癌治疗指南接受辅助化疗。针对化疗引起的消化道反应,对照组患者由经治医师开处常规对症治疗药物,而干预组患者所接受的对症治疗方案由临床药师和经治

医师共同研究制定。化疗期间,临床药师定期对患者进行咨询,详细记录用药情况,并根据治疗反应及时调整对症治疗方案并将信息反馈给经治医师,如两者意见一致则按照调整方案用药,如出现分歧提请上级医师裁决是否调整对症治疗方案。药师咨询过程中主要向患者讲解化疗用药方案、药物潜在毒副反应和预防策略,重点讲解止吐治疗的必要性、药物的用法和剂量。

### 1.3 观测指标

主要观测患者化疗开始后对于止吐药物的完全反缓解率、恶心程度、呕吐频率。化疗开始 5 天内无呕吐定义为完全缓解,恶心程度和呕吐频率分别由整个监测周期内患者发生急性或迟发性恶心和呕吐的积分之和除以化疗周期数代表。此外,通过 EORTC QLQ-C30 生活质量测评量表于化疗前(基线)和第 3 周期结束 1 周后监测患者生活质量评分,计算前后差值,比较两组间生活质量变化情况<sup>[3]</sup>。

### 1.4 统计学方法

采用 SPSS13.0 统计软件进行分析。计数资料采用卡方检验,恶心程度、呕吐频率和生活质量评分采用非参数检验。 $P<0.05$  有统计学意义。

## 2 结果

### 2.1 患者基线临床病理特点

患者临床病理特点见(表 1)。两组患者在年龄、肿瘤分期(TNM)、病理类型、手术方式、化疗方案、靶向治疗情况等方面分布均衡,差异无统计学意义。

表 1 患者基线临床病理特点  
Table 1 Clinicopathological characteristics of patients at baseline

| Items                | Control | Intervention | P     |
|----------------------|---------|--------------|-------|
|                      | n=43    | n=44         |       |
| Aeg (Mean, Range)    | <30     | 3            | 0.806 |
| 31-40                | 9       | 8            |       |
| 41-50                | 13      | 17           |       |
| 51-60                | 15      | 12           |       |
| >60                  | 3       | 2            |       |
| Stage                |         |              | 0.861 |
| I                    | 6       | 5            |       |
| II                   | 23      | 26           |       |
| III                  | 14      | 13           |       |
| Histological type    |         |              | 0.744 |
| Lobular invasive     | 12      | 15           |       |
| Ductal invasive      | 25      | 22           |       |
| Others               | 6       | 7            |       |
| Chemotherapy regimen |         |              |       |
| EC                   | 4       | 5            |       |
| FEC                  | 10      | 12           |       |

续表

|                             |    |    |       |
|-----------------------------|----|----|-------|
| EC-T                        | 5  | 4  |       |
| EC-D                        | 10 | 11 |       |
| AC                          | 5  | 3  |       |
| FEC-D                       | 7  | 8  |       |
| PC                          | 2  | 1  | 0.969 |
| Surgery                     |    |    |       |
| Extensive dical mastectomy  | 4  | 5  |       |
| Modified radical mastectomy | 35 | 32 |       |
| Lumpectomy                  | 4  | 7  | 0.591 |
| Combined target therapy     |    |    |       |
| Yes                         | 4  | 3  |       |
| No                          | 39 | 41 | 0.670 |

## 2.2 消化道反应的完全缓解率

化疗的前3个周期两组对止吐药物的完全缓解率(Complete response, CR)分别为37.2%和63.6%,46.5%和75.0%,

44.2%和72.7%,干预组患者的完全缓解率明显高于对照组患者( $P=0.014$ ,  $P=0.006$ ,  $P=0.007$ ),显示药学干预可明显提高患者消化道反应对症治疗的完全缓解率(表2)。

表2 患者呕吐完全缓解率(%)

Table 2 Number of patients with or without "CR emesis" (in percent)

|        | Control group |          |          | Intervention group |          |          | P     |
|--------|---------------|----------|----------|--------------------|----------|----------|-------|
|        | N             | CR       | No CR    | N                  | CR       | No CR    |       |
| Cycle1 | 43            | 16(37.2) | 27(62.8) | 44                 | 28(63.6) | 16(36.4) | 0.014 |
| Cycle2 | 43            | 20(46.5) | 23(53.5) | 44                 | 33(75.0) | 11(25.0) | 0.006 |
| Cycle3 | 43            | 19(44.2) | 24(55.8) | 44                 | 32(72.7) | 12(27.3) | 0.007 |

## 2.3 恶心程度和呕吐频率

如表3所示,干预组患者的急性和延迟性恶心程度分别为3.4和4.2,对照组患者的急性和延迟性恶心程度分别为9.5和9.6,干预组患者恶心程度较对照组患者明显减轻。干预组患者

急性和延迟性呕吐频率分别为1.3和0.2,对照组则分别为3.8和0.7,干预组患者呕吐频率也较对照组患者减少,差异具有统计学意义。

表3 恶心呕吐的严重程度和频率

Table 3 Severity and frequency of nausea and vomiting

|         | Control group |        |           | Intervention group |        |           | P     |
|---------|---------------|--------|-----------|--------------------|--------|-----------|-------|
|         | N             | Median | Quartiles | N                  | Median | Quartiles |       |
| Nausea  |               |        |           |                    |        |           |       |
| Acute   | 43            | 9.5    | 7.2;17.9  | 44                 | 3.4    | 0.9;6.8   | 0.023 |
| Delayed | 43            | 9.6    | 1.8;18.6  | 44                 | 4.2    | 1.2;11.5  | 0.045 |
| Vomit   |               |        |           |                    |        |           |       |
| Acute   | 43            | 0.8    | 0.5;2.8   | 44                 | 0.2    | 0;0.3     | 0.006 |
| Delayed | 43            | 0.3    | 0.1;0.9   | 44                 | 0.1    | 0;0.2     | 0.034 |

## 2.4 生活质量

EORTC QLQ-C30生活质量测评量表包括总健康状况评分和症状及功能领域评分。表4显示了患者从基线到第3周期化疗结束后所有测评项目前后评分变化情况。其中干预组患者

总健康状况评分较对照组明显提高( $P=0.028$ ),恶心、呕吐和食欲丧失的症状评分较对照组降低( $P=0.025$ ,  $P=0.045$ ),差异具有统计学意义,提示药学干预具有积极作用。

## 3 讨论

表 4 基线至化疗结束生活质量改善绝对值变化

Table 4 Absolute change of quality of life from baseline to the end of chemotherapy

| Item | Control group |             | Intervention group |             | P value |
|------|---------------|-------------|--------------------|-------------|---------|
|      | Median        | Quartiles   | Mean               | Quartiles   |         |
| DY   | 16.7          | 0;33.3      | 0                  | 0;33.3      | 0.851   |
| PA   | 0             | -16.7;26.8  | 0                  | -16.7;33.3  | 0.257   |
| FA   | 21.2          | 0;35.4      | 17.8               | 0;22.8      | 0.326   |
| SL   | 8.3           | 0;24.2      | 12.9               | 0;23.3      | 0.694   |
| AL   | 16.7          | 0;66.7      | 0                  | -16.7;33.3  | 0.045   |
| NV   | 33.3          | 12.4;50     | 16.7               | 0;33.3      | 0.025   |
| CO   | 33.3          | 0;33.3      | 16.7               | 0;33.3      | 0.112   |
| DI   | 0             | -7.4;9.8    | 0                  | -12.6;16.7  | 0.754   |
| PF   | -13.3         | -15.6;5.0   | -6.7               | -16.7;8.3   | 0.296   |
| RF   | 11.1          | -33.3;-16.7 | 8.6                | -33.3;-16.7 | 0.574   |
| CF   | 0             | -33.3;-16.7 | -8.3               | -16.7;16.7  | 0.168   |
| EF   | -61.2         | -87.3;-43.7 | -61.7              | -82.4;-41.6 | 0.746   |
| SF   | 0             | -33.3;16.7  | 0                  | -16.7;8.7   | 0.066   |
| FI   | 7.3           | 6.8;13.2    | 3.3                | 8.2;11.3    | 0.432   |
| GH   | -7.6          | -24.8;1.3   | 1.1                | -15.4;10.4  | 0.028   |

注: DY: dyspnea, 呼吸困难 PA: pain, 疼痛 FA: fatigue, 疲劳 SL: sleeplessness, 失眠 AL: appetite loss, 食欲丧失 NV: nausea/vomiting, 恶心 / 呕吐 CO: constipation, 便秘 DI: diarrhea, 腹泻 PF: physical functions, 躯体功能 RF: role functions, 角色功能 CF: cognitive functions, 认知功能 EF: emotion functions, 情感功能 SF: social functions, 社会功能 FI: financial impact, 经济影响 GH: global health, 总健康状况

肿瘤患者的治疗药物种类繁多、作用机制不一,其治疗需高度个体化。抗肿瘤治疗通常伴随许多严重的药物不良反应,因此越来越需要有效的对症支持和药学护理,以预防或减缓不良反应发生<sup>[4-8]</sup>。近 10 年来基于循证医学数据,关于支持治疗和护理相继推出了多项临床实践指南,抗肿瘤治疗的同时进行对症支持治疗已成为共识并在临床逐步完善和规范<sup>[9]</sup>。然而,抗肿瘤药物引起的不良反应发生率仍然居高不下。化疗引起的恶心、呕吐已成为乳腺癌患者治疗期间无可避免的毒副反应。大量研究表明,预防性给药可以有效降低化疗引起的恶心和呕吐反应,但是抗肿瘤治疗相关的毒副反应仍然较难预防和控制,这与医师未能完全遵照预防呕吐治疗指南用药不无关联<sup>[9-12]</sup>。Mertens<sup>[13]</sup>等开展的一项研究发现,临床医师在遵循指南处理化疗引发的呕吐时不够彻底,主要是对延迟性呕吐的处理规范执行不够。当患者的症状信息通过设计的统计表格由护理人员反馈给医生后,医生会意识到治疗不足并调整用药,患者的恶心、呕吐症状特别是延迟性呕吐可明显改善。

药学干预或护理是临床药师为增强疗效和改善生活质量而对医师提供的用药方面的指导和建议。肿瘤患者的医护人员中加入药师,可以促进合理用药,并最大限度提高医师和患者对规范的用药指南的执行力 and 依从性。药学干预在国外开展的已经比较广泛。Caracul<sup>[14]</sup>等探讨了药学护理干预对成人患者化疗引发的延迟性恶心和呕吐发生率的影响,该前瞻性队列研究的研究对象均是 102 例新接受静脉化疗的肿瘤患者,药学干预手段包括药师审查止吐治疗流程并给患者一些建议。结果显

示,药学干预组患者延迟性呕吐完全缓解率达到 84.4%,而对照组则为 69.6%,绝对风险下降 15.2%;未发生呕吐的比率在药学干预组为 97.0%,对照组为 71.0%;未发生延迟性恶心的比率在药学干预组和对照组分别为 61%和 52%,结论认为药学干预可以提高用药规范和依从性,减少化疗引起的延迟性呕吐。与上述研究一致,我们开展的研究发现乳腺癌患者化疗时对止吐药物实施药学干预后,呕吐完全缓解率可从 37.2%提高到 63.6%,而且此后每周期化疗均有同样趋势。干预组的急性和迟发性恶心也较对照组明显减轻,发生频率也较对照组明显减少。可能是由于患者人种、化疗方案不同,我们的数据与上述报道有一定差异,但药学干预改善患者恶心和呕吐的效果都是显著的。

肿瘤患者的药学干预并非仅仅针对化疗药物引发的毒副反应,还可以加以推广应用。比如对吗啡等其他常用药物的毒副反应进行干预处理。Ishihara<sup>[15]</sup>等对比了药师药学干预前后临床医师对吗啡引发呕吐、便秘的预防性药物处理的效果差异。结果显示,在药学干预前,临床医师对吗啡引发的呕吐和便秘进行预防用药处理的比率仅为 52%和 57%,由于处理不够导致便秘 (OR,5.25; 95% CI,1.93-14.31;P=0.001) 和呕吐 (4.67, 1.04-21.04;P=0.045)发生风险增加。当实施药学干预措施(包括向医师提供用药信息、审核医师药物处方、向患者提供用药咨询)后,医师对便秘和呕吐采取药物处理的比率分别达到 93%和 81%。患者便秘的发生率从 36%下降到 9%,恶心发生率从 28%下降到 17%,呕吐发生率从 16%下降到 4%,结论认为药

学干预可以提高针对吗啡不良反应所采取的预防性给药的有效率,降低患者发生恶心呕吐和便秘的风险。

对肿瘤患者实施药学干预可有效减轻化疗及其他药物的不良反应外,还可以显著提高患者生活质量。本研究生活质量测评结果显示干预组患者总健康状况较对照组升高,恶心、呕吐和食欲丧失的症状评分较对照组降低。Liekweg<sup>[16]</sup>等开展的前瞻性多中心研究也证实了我们的结论。该研究纳入了98例乳腺癌和卵巢癌患者,48例患者化疗时仅接受规范的对症治疗和护理,50例患者除上述治疗和护理外还要接受药学干预。结果显示,药学干预组恶心呕吐的完全缓解率较对照组明显提高,且生活质量也显著改善。

总之,肿瘤治疗正在向个体化用药发展,同时也迫切需要多学科协作,在处里抗肿瘤治疗相关毒副反应中如何实施多学科协作也自然成为现实需求<sup>[17,18]</sup>。临床医师主要关注于诊断和治疗方案的有效性,而护理人员则侧重于正确执行医嘱,临床药师界于两者之间加之其专业优势使其对药物不良反应把握更为准确,开展药学干预、增强与患者的用药沟通,可有效提高药物治疗的效果,预防不良反应发生并改善生活质量<sup>[19,20]</sup>。本研究探索了临床药师干预对乳腺癌患者辅助化疗期间恶心呕吐和生活质量的影响,结果提示药师干预可明显缓解患者的上述消化道不良反应,明显改善了生活质量,取得了良好效果。这为今后加强对肿瘤患者药学干预以降低抗肿瘤治疗毒副反应、改善患者的生存预后和生活质量提供了临床证据,也对规范医护人员临床用药具有重要意义。

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