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· 论 著 ·

神经激肽 1 受体拮抗剂替代地塞米松二联方案预防中度致吐风险化疗所致恶心呕吐的随机对照试验

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[摘要] **目的** 比较神经激肽 1 (NK-1) 受体拮抗剂 (RA) 联合托烷司琼与地塞米松联合托烷司琼预防中度致吐风险化疗所致恶心呕吐 (MEC-CINV) 的效果。**方法** 采用非劣效性试验设计, 将中国人民解放军南部战区总医院肿瘤科 2021 年 4 月至 2022 年 1 月满足条件的拟接受中度致吐风险化疗的肿瘤患者按照随机数字表法分为 NK-1 RA 组和地塞米松组。NK-1 RA 组患者采用 NK-1 RA (阿瑞匹坦或福沙匹坦) + 托烷司琼二联止吐方案, 地塞米松组采用托烷司琼 + 地塞米松标准二联止吐方案。主要评价指标为总观察期 (0~120 h)、延迟期 (24~120 h)、急性期 (24 h 内) 的呕吐完全缓解 (CR) 率, 次要评价指标为各期恶心完全控制 (CC) 率及恶心呕吐总缓解 (TR) 率, 安全性指标为止吐药物的不良反应 (包括乏力、便秘、呃逆、失眠等症状指标, 以及白细胞计数减少、中性粒细胞计数减少、血红蛋白下降、血小板计数减少、丙氨酸转氨酶和/或天冬氨酸转氨酶升高、血肌酐升高等实验室指标异常)。采用差异性检验 (检验水准为 0.05) 和非劣效性检验 (非劣效性界值为 15%, 检验水准为 0.025) 比较两组的干预效果。**结果** 最终共有 101 例患者全程参与本研究, 其中 NK-1 RA 组 51 例, 地塞米松组 50 例。NK-1 RA 组和地塞米松组总观察期呕吐 CR 率分别为 58.8% (30/51) 和 56.0% (28/50), 非劣效性检验无统计学意义 [$P_{非劣效}=0.035$, 率差 (RD)=2.80%, 95% CI -16.5%~22.1%]; 急性期呕吐 CR 率分别为 80.4% (41/51) 和 78.0% (39/50), 非劣效性检验有统计学意义 ($P_{非劣效}=0.016$, RD=2.40%, 95% CI -13.4%~18.2%); 延迟期呕吐 CR 率分别为 62.7% (32/51) 和 58.0% (29/50), 非劣效性检验有统计学意义 ($P_{非劣效}=0.021$, RD=4.70%, 95% CI -14.4%~23.8%)。NK-1 RA 组各期恶心 CC 率略高于地塞米松组, 非劣效性检验有统计学意义 (均 $P_{非劣效}<0.025$)。两组间各安全性指标差异无统计学意义 (均 $P>0.05$)。**结论** 在 MEC-CINV 患者中, NK-1 RA 联合托烷司琼的二联止吐方案对恶心呕吐的控制效果非劣效于地塞米松联合托烷司琼标准二联止吐方案, 且安全性良好。

[关键词] 中度致吐风险化疗; 恶心; 呕吐; 5-羟色胺 3 受体拮抗剂; 神经激肽 1 受体拮抗剂; 地塞米松

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Neurokinin-1 receptor antagonist as an alternative to dexamethasone in standard dual regimen for moderately emetogenic chemotherapy-induced nausea and vomiting: a randomized controlled trial

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[Abstract] **Objective** To compare the effects of neurokinin-1 (NK-1) receptor antagonist (RA) plus tropisetron versus dexamethasone plus tropisetron against moderately emetogenic chemotherapy-induced nausea and vomiting (MEC-CINV). **Methods** A non-inferiority trial was designed. Patients who received moderately emetogenic chemotherapy in Department of Oncology of General Hospital of Southern Theater Command of PLA from Apr. 2021 to Jan. 2022 were randomly assigned to NK-1 RA (NK-1 RA + tropisetron) group or dexamethasone (tropisetron + dexamethasone) group by random number table method. Primary evaluation indexes were complete response (CR) rates of vomiting at overall phase (0-120 h), delayed phase (24-120 h) and acute phase (<24 h). Secondary evaluation indexes were complete control (CC) rate of nausea and total response (TR) rate of nausea and vomiting at each phase. Safety indexes were adverse events (symptoms such as fatigue, constipation, hiccup and insomnia; abnormal laboratory indicators such as decline of leukocyte, neutrophil, hemoglobin and platelet and increase of alanine transaminase and/or aspartate transaminase and serum creatinine). The

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intervention effects of the 2 groups were compared by difference test (test level was 0.05) and non-inferiority test (non-inferiority margin was 15%, and test level was 0.025). **Results** A total of 101 patients participated in the study, including 51 in the NK-1 RA group and 50 in the dexamethasone group. The CR rates of vomiting at overall phase in the NK-1 RA group and dexamethasone group were 58.8% (30/51) and 56.0% (28/50), respectively, and non-inferiority test showed no statistical significance ($P_{\text{non-inferiority}}=0.035$, rate difference [RD]=2.80%, 95% confidence interval [CI] -16.5%-22.1%); the CR rates of vomiting at acute phase were 80.4% (41/51) and 78.0% (39/50), respectively, and non-inferiority test was statistically significant ($P_{\text{non-inferiority}}=0.016$, RD=2.40%, 95% CI -13.4%-18.2%); and the CR rates of vomiting at delayed phase were 62.7% (32/51) and 58.0% (29/50), respectively, and non-inferiority test was statistically significant ($P_{\text{non-inferiority}}=0.021$, RD=4.70%, 95% CI -14.4%-23.8%). The CC rate of nausea at each phase was slightly higher in the NK-1 RA group than that in the dexamethasone group, and the non-inferiority test was statistically significant (all $P_{\text{non-inferiority}}<0.025$). There was no significant difference in the safety indicators between the 2 groups (all $P>0.05$). **Conclusion** In MEC-CINV patients, the control effect of antiemetic regimen of NK-1 RA combined with tropisetron on nausea and vomiting is non-inferior to the standard dual regimen dexamethasone combined with tropisetron, and the safety is good.

[**Key words**] moderately emetogenic chemotherapy; nausea; vomiting; 5-hydroxytryptamine 3 receptor antagonist; neurokinin-1 receptor antagonist; dexamethasone

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恶心和呕吐是化疗期间常见的不良反应, 如果化疗期间不进行预防性止吐干预, 70%~80%的患者会出现化疗所致恶心呕吐 (chemotherapy-induced nausea and vomiting, CINV), 对CINV控制不佳可直接影响患者抗肿瘤治疗的整体预后^[1]。糖皮质激素、5-羟色胺3 (5-hydroxytryptamine 3, 5-HT₃) 受体拮抗剂 (receptor antagonist, RA) 和神经激肽1 (neurokinin-1, NK-1) RA是高-中度致吐风险化疗期间的常用止吐药物。对于高度致吐风险化疗 (highly emetogenic chemotherapy, HEC), 指南推荐的一线止吐方案为5-HT₃ RA、NK-1 RA和地塞米松三联疗法; 而对于中度致吐风险化疗 (moderately emetogenic chemotherapy, MEC), 各指南将5-HT₃ RA联合地塞米松的二联止吐方案作为一线推荐, 5-HT₃ RA、NK-1 RA和地塞米松的三联方案只在同时合并恶心与呕吐高危因素的患者中使用^[1-2]。地塞米松会给患者带来诸多不良反应, 尤其是应用于患有糖尿病、胃溃疡等基础疾病的患者时更应谨慎^[3-4], 且地塞米松有免疫抑制作用, 长期使用可能影响肿瘤免疫治疗的效果^[5]。因此, 开展去糖皮质激素止吐方案的临床探索非常必要。目前大多研究聚焦于HEC, 对MEC导致的呕吐能否使用NK-1 RA替代地塞米松研究尚少。本研究比较了NK-1 RA联合托烷司琼的二联止吐方案与地塞米松联合托烷司琼的标准一线二联止吐方案对MEC-CINV的预防效果, 为MEC-CINV的去

糖皮质激素化防治提供参考依据。

1 资料和方法

1.1 研究对象 本研究是一项单中心前瞻性探索性研究, 已通过中国人民解放军南部战区总医院伦理委员会审批 (院伦理 2021 [28])。参考验证性研究非劣效性试验的样本量估算方法, 综合既往研究和预试验结果, 按照试验组与阳性对照组样本量1:1的比例纳入参与者, 主要观察指标设置为总观察期试验组完全缓解 (complete response, CR) 率42.6%、阳性对照组CR率66.9%, 检验水准 (α) 设置为0.05 (相当于非劣效性试验 $\alpha=0.025$), 检验效能 ($1-\beta$) 设置为0.8, 非劣效性界值 Δ 为15%, 失访率5%, 将以上数值代入统计平台在线工具 (www.medsta.cn, 浙江中医药大学) 进行估算, 得到每组样本量至少25例。用SPSS 15软件生成随机数字, 将中国人民解放军南部战区总医院肿瘤科2021年4月至2022年1月满足纳入条件的患者随机分配至试验组和阳性对照组。

纳入标准: (1) 性别不限, 年龄 ≥ 18 岁, 经病理确诊为恶性肿瘤, 拟接受MEC方案治疗 [MED方案包括奥沙利铂+卡培他滨 (XELOX)、5-氟尿嘧啶+亚叶酸钙+奥沙利铂 (FOLFOX)、5-氟尿嘧啶+亚叶酸钙+伊立替康+奥沙利铂 (FOLFIRINOX)、白蛋白紫杉醇+奈达铂/卡铂 (总铂浓度-时间AUC值 <4 mg/mL·min) 等];

(2) Karnofsky 体力状态评分为 70~100 分或美国东部肿瘤协作组 (Eastern Cooperative Oncology Group, ECOG) 评分为 0~2 分; (3) 化疗前肝肾功能、血常规、心电图等检查未发现明显异常 (血肌酐 < 正常参考值上限 1.5 倍, 总胆红素 < 正常参考值上限 1.5 倍, 丙氨酸转氨酶 < 正常参考值上限 2.5 倍, 碱性磷酸酶 < 正常参考值上限 2.5 倍, 血小板计数 $> 85 \times 10^9/L$, 中性粒细胞计数 $> 1.5 \times 10^9/L$, 白细胞计数 $> 3.5 \times 10^9/L$, 红细胞计数 $> 2 \times 10^{12}/L$, 血红蛋白 $> 80 g/L$), 无化疗禁忌证; (4) 入组前 1 周至化疗前 1 d 无明显恶心呕吐症状; (5) 预计生存期为 3 个月以上; (6) 理解本研究方案, 自愿参加本研究并签署知情同意书。

排除标准: (1) 有长期使用糖皮质激素史; (2) 化疗前 24 h 出现过呕吐; (3) 妊娠或哺乳期女性; (4) 对 5-HT₃ RA、NK-1 RA 或地塞米松过敏; (5) 其他非肿瘤因素所致的恶心呕吐或正在服用其他致吐性药物或酒精中毒者; (6) 用药方案中包含多西他赛注射液、紫杉醇注射液、紫杉醇脂质体注射液、培美曲塞注射液、西妥昔单抗注射液、利妥昔单抗注射液等经临床医师判断需使用地塞米松做化疗前预处理的药物。

剔除标准: (1) 各种因素导致未顺利完成 1 个周期化疗和止吐治疗者; (2) 各种因素所致无法完成随访者。

1.2 止吐方案 试验组 (NK-1 RA 组) 患者予 NK-1 RA + 托烷司琼二联止吐方案, 阳性对照组 (地塞米松组) 患者予托烷司琼 + 地塞米松标准一线二联止吐方案。NK-1 RA 给药方案: 福沙匹坦于第 1 天静脉滴注 150 mg 1 次, 或阿瑞匹坦于第 1 天口服 125 mg 1 次、第 2 天和第 3 天各口服 80 mg 1 次; 地塞米松给药方案: 于第 1~3 天每天静脉滴注 5 mg 1 次; 托烷司琼给药方案: 于第 1~3 天每天静脉滴注 5 mg 1 次。

1.3 疗效评价 疗效观察期为化疗开始前 1 d 至化疗结束后第 5 天, 观察两组间化疗后急性期 (24 h 内)、延迟期 (24~120 h) 及总观察期 (0~120 h) CINV 治疗有效率及不良反应发生率。患者填写国际癌症支持治疗协会止吐评价量表, 评估 CINV 发生情况^[1]。(1) 主要评价指标为总观察期、延迟期及急性期获得的呕吐 CR 率。呕吐 CR 定义为没有呕吐或干呕发作、无明显恶心 (视觉模拟量表评

分 ≤ 4 分) 且不使用救援药物。(2) 次要评价指标为总观察期、延迟期及急性期获得的恶心完全控制 (complete control, CC) 率和恶心呕吐总缓解 (total response, TR) 率。恶心 CC 定义为没有呕吐或干呕发作、无中至重度恶心且不使用救援药物, 恶心呕吐 TR 定义为没有呕吐或干呕发作、无恶心且不使用救援药物^[5-6]。(3) 安全性指标: 观察并记录止吐药物的不良反应, 包括乏力、便秘、呃逆、失眠等症状, 以及白细胞计数减少、中性粒细胞计数减少、血红蛋白下降、血小板计数减少、丙氨酸转氨酶和 / 或天冬氨酸转氨酶升高、血肌酐升高等实验室指标异常, 采用美国国家癌症研究所常见不良事件评价标准 (National Cancer Institute Common Terminology Criteria for Adverse Events, NCI-CTCAE) 5.0 进行评价。

1.4 统计学处理 采用 SPSS 25.0 软件进行统计学分析。两组的基线资料为二分类和多分类资料, 以例数和百分数表示, 组间比较采用 χ^2 检验, 当不满足 χ^2 检验条件时采用连续校正的 χ^2 检验或 Fisher 确切概率法, 检验水准 (α) 为 0.05。主要和次要评价指标为分类资料, 以例数和百分数表示, 组间比较采用 χ^2 检验; 当差异性检验没有统计学意义 ($P > 0.05$) 但具有其他的临床优点时, 进一步行非劣效性检验。计算两组率差 (rate difference, RD) 的 95% CI, 当 RD 95% CI 的下限包含在非劣效性界值 Δ 区间 (-15%~15%) 内, 同时非劣效 P 值 ($P_{\text{非劣效}}$) < 0.025 (单侧) 时认为非劣效性检验具有统计学意义。根据两组患者的肿瘤类型, 各分为消化系统肿瘤与非消化系统肿瘤两个亚组, 采用 Cochran-Mantel-Haenszel (CMH) 检验进行分层分析, 计算 OR 及其 95% CI, 并采用 Breslow-Day 和 Tarone's 检验对不同分层的 OR 进行一致性检验; 当分层 $P > 0.05$ 时, 可判断组间基线不平衡对疗效评价指标的评估没有明显影响。不良反应事件发生率为有序多分类变量, 以例数和百分数表示, 组间比较采用 Mann-Whitney U 检验, 检验水准 (α) 为 0.05。

2 结果

2.1 基线资料 本临床试验研究结果的报告遵循临床试验报告的统一标准 (Consolidated Standards of Reporting Trials, CONSORT) 2010。排除 3 例, 因随访丢失剔除 1 例, 最终共有 101 例 (NK-1

RA组51例、地塞米松组50例)患者全程参与本研究,均顺利完成观察周期的化疗及止吐方案,依从性及耐受性较好。临床试验报告流程图见图1。除肿瘤类型外,两组患者的性别、年龄、

ECOG评分、TNM分期、MEC化疗用药天数、化疗史、MEC化疗药物等特征差异均无统计学意义(均 $P>0.05$,表1)。

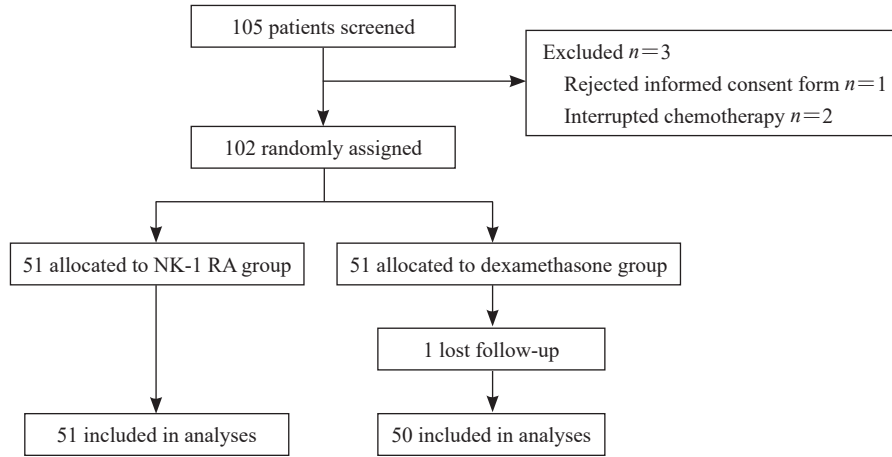


图1 临床试验报告流程图

Fig 1 Flow chart for clinical trial reporting

The patients in the NK-1 RA group received NK-1 RA+tropisetron and those in the dexamethasone group received tropisetron+dexamethasone. NK-1: Neurokinin-1; RA: Receptor antagonist.

表1 两组患者的基线特征

Tab 1 Baseline characteristics of 2 groups

Characteristic	NK-1 RA group N=51	Dexamethasone group N=50	χ^2 value	<i>n</i> (%) <i>P</i> value
Gender			0.095	0.758
Male	27 (52.9)	28 (56.0)		
Female	24 (47.1)	22 (44.0)		
Age/year			0.080	0.777
<50	19 (37.3)	20 (40.0)		
≥50	32 (62.7)	30 (60.0)		
ECOG score			0.001 ^a	0.978 ^a
0-1	48 (94.1)	46 (92.0)		
2	3 (5.9)	4 (8.0)		
Tumor type			9.135	0.003
Gastrointestinal cancer	25 (49.0)	39 (78.0)		
Other cancers	26 (51.0)	11 (22.0)		
Days of chemotherapy			0.079	0.778
Single-day	16 (31.4)	17 (34.0)		
Multi-day	35 (68.6)	33 (66.0)		
TNM classification			0.378	0.539
I - III	15 (29.4)	12 (24.0)		
IV	36 (70.6)	38 (76.0)		
Chemotherapy history			0.083	0.774
Yes	39 (76.5)	37 (74.0)		
No	12 (23.5)	13 (26.0)		
MEC agent			0.238	0.626
Oxaliplatin	19 (37.3)	21 (42.0)		
Non-oxaliplatin	32 (62.7)	29 (58.0)		

The patients in the NK-1 RA group received NK-1 RA+tropisetron and those in the dexamethasone group received tropisetron+dexamethasone. ^a: Continuity correction χ^2 test. NK-1: Neurokinin-1; RA: Receptor antagonist; ECOG: Eastern Cooperative Oncology Group; MEC: Moderately emetogenic chemotherapy.

2.2 CINV 疗效评价 所有患者均顺利完成 1 个周期的治疗。NK-1 RA 组和地塞米松组的呕吐 CR 率在总观察期分别为 58.8% 和 56.0%，在急性期分别为 80.4% 和 78.0%，在延迟期分别为 62.7% 和 58.0%。 χ^2 检验结果显示，两组间各期呕吐 CR 率差异无统计学意义（均 $P > 0.05$ ）。非劣效性检验

结果显示，两组总观察期呕吐 CR 率无统计学意义（ $P_{\text{非劣效}} = 0.035$ ），两组急性期和延迟期呕吐 CR 率均有统计学意义（ $P_{\text{非劣效}} = 0.016$ 、 $P_{\text{非劣效}} = 0.021$ ），表明 NK-1 RA + 托烷司琼二联止吐方案在急性期和延迟期对呕吐症状的控制效果与托烷司琼 + 地塞米松标准二联止吐方案相比具有非劣效性。见表 2。

表 2 两组患者各疗效观察期呕吐 CR 率的比较

Tab 2 Comparison of CR rates of vomiting at different curative observation phases between 2 groups

Phase	NK-1 RA group N=51	Dexamethasone group N=50	χ^2 test		Non-inferiority test ^a	
					n (%)	
			χ^2 value	P value	RD (95% CI)/%	$P_{\text{non-inferiority}}$ value
Acute (0-<24 h)	41 (80.4)	39 (78.0)	0.088	0.767	2.40 (-13.4, 18.2)	0.016
Delayed (24-120 h)	32 (62.7)	29 (58.0)	0.238	0.626	4.70 (-14.4, 23.8)	0.021
Overall (0-120 h)	30 (58.8)	28 (56.0)	0.082	0.774	2.80 (-16.5, 22.1)	0.035

The patients in the NK-1 RA group received NK-1 RA + tropisetron and those in the dexamethasone group received tropisetron + dexamethasone. ^a: The lower bound of 95% CI of RD included in Δ interval (-15%-15%) and $P_{\text{non-inferiority}} < 0.025$ (one-sided), indicating that non-inferiority test was statistically significant. CR: Complete response; NK-1: Neurokinin-1; RA: Receptor antagonist; RD: Rate difference; CI: Confidence interval; Δ : Non-inferiority margin.

NK-1 RA 组和地塞米松组的恶心 CC 率在总观察期分别为 47.1% 和 36.0%，在急性期分别为 72.5% 和 64.0%，在延迟期分别为 49.0% 和 42.0%。 χ^2 检验结果显示，两组间各期恶心 CC 率差异无统计学意义（均 $P > 0.05$ ）。非劣效性检验结果显示，两组间各期恶心 CC 率均有统计学意义（ $P_{\text{非劣效}} = 0.004$ 、 0.005 、 0.013 ），表明 NK-1 RA + 托烷司琼二联止吐方案在总观察期、急性期和延迟期对恶心症状的控制效果与托烷司琼 + 地塞米松标准二联止吐方案相比具有非劣效性。NK-1 RA 组和地塞米松组的恶心呕吐

TR 率在总观察期分别为 29.4% 和 28.0%，在急性期分别为 62.7% 和 54.0%，在延迟期分别为 31.4% 和 30.0%。 χ^2 检验结果显示，两组间各期恶心呕吐 TR 率差异无统计学意义（均 $P > 0.05$ ）。非劣效性检验结果显示，两组总观察期和延迟期恶心呕吐 TR 率无统计学意义（ $P_{\text{非劣效}} = 0.034$ 、 0.037 ），急性期恶心呕吐 TR 率具有统计学意义（ $P_{\text{非劣效}} = 0.008$ ），表明 NK-1 RA + 托烷司琼二联止吐方案在急性期对恶心呕吐发作的控制效果与托烷司琼 + 地塞米松标准二联止吐方案相比具有非劣效性。见表 3。

表 3 两组患者各疗效观察期恶心 CC 率和恶心呕吐 TR 率的比较

Tab 3 Comparison of CC rates of nausea and TR rates of nausea and vomiting at different curative observation phases between 2 groups

Index	NK-1 RA group N=51	Dexamethasone group N=50	χ^2 test		Non-inferiority test ^a	
					n (%)	
			χ^2 value	P value	RD (95% CI)/%	$P_{\text{non-inferiority}}$ value
CC rate of nausea						
Acute (0-<24 h)	37 (72.5)	32 (64.0)	0.853	0.356	8.50 (-9.6, 26.6)	0.005
Delayed (24-120 h)	25 (49.0)	21 (42.0)	0.502	0.479	7.00 (-12.4, 26.4)	0.013
Overall (0-120 h)	24 (47.1)	18 (36.0)	1.271	0.260	11.1 (-8.0, 30.2)	0.004
TR rate of nausea and vomiting						
Acute (0-<24 h)	32 (62.7)	27 (54.0)	0.795	0.373	8.70 (-10.5, 27.9)	0.008
Delayed (24-120 h)	16 (31.4)	15 (30.0)	0.022	0.881	1.40 (-16.6, 19.4)	0.037
Overall (0-120 h)	15 (29.4)	14 (28.0)	0.025	0.875	1.40 (-16.3, 19.0)	0.034

The patients in the NK-1 RA group received NK-1 RA + tropisetron and those in the dexamethasone group received tropisetron + dexamethasone. ^a: The lower bound of 95% CI of RD included in Δ interval (-15%-15%) and $P_{\text{non-inferiority}} < 0.025$ (one-sided), indicating that non-inferiority test was statistically significant. CC: Complete control; TR: Total response; NK-1: Neurokinin-1; RA: Receptor antagonist; RD: Rate difference; CI: Confidence interval; Δ : Non-inferiority margin.

2.3 不同肿瘤类型对疗效影响的分层分析 将两组患者分别分为消化系统肿瘤与非消化系统肿瘤两个亚组, χ^2 检验结果显示分层后两组各疗效观察期的呕吐 CR 率、恶心 CC 率和恶心呕吐 TR 率差异均无统计学意义 (均 $P>0.05$, 表 4), CMH 检验

结果显示分层后两组间各疗效观察期 OR 的 95% CI 范围较大且均包含 1 (均 $P>0.05$, 表 5)。结果表明, 不同肿瘤类型在两组间的基线不均衡对评价指标没有明显影响。

表 4 按肿瘤类型分层后两组患者各疗效观察期治疗结果比较

Tab 4 Comparison of outcomes at different curative observation phases between 2 groups after stratification by tumor types

Outcome	Phase	Tumor type	NK-1 RA group		Dexamethasone group		χ^2 value	<i>n</i> (%)
			<i>N</i>	CR/CC/TR rate	<i>N</i>	CR/CC/TR rate		
CR of vomiting	Acute (0-<24 h)	Gastrointestinal	25	21 (84.0)	39	31 (79.5)	0.015 ^a	0.902 ^a
		Others	26	20 (76.9)	11	8 (72.7)	0.026 ^a	0.883 ^a
	Delayed (24-120 h)	Gastrointestinal	25	18 (72.0)	39	21 (53.8)	2.109	0.146
		Others	26	14 (53.8)	11	8 (72.7)	0.494 ^a	0.482 ^a
	Overall (0-120 h)	Gastrointestinal	25	16 (64.0)	39	21 (53.8)	0.644	0.422
		Others	26	14 (53.8)	11	7 (63.6)	0.035 ^a	0.852 ^a
CC of nausea	Acute (0-<24 h)	Gastrointestinal	25	19 (76.0)	39	26 (66.7)	0.636	0.425
		Others	26	18 (69.2)	11	6 (54.5)	0.229 ^a	0.632 ^a
	Delayed (24-120 h)	Gastrointestinal	25	15 (60.0)	39	14 (35.9)	3.571	0.059
		Others	26	10 (38.5)	11	7 (63.6)	1.973	0.160
	Overall (0-120 h)	Gastrointestinal	25	14 (56.0)	39	14 (35.9)	2.241	0.134
		Others	26	10 (38.5)	11	4 (36.4)	0.063 ^a	0.802 ^a
TR of nausea and vomiting	Acute (0-<24 h)	Gastrointestinal	25	15 (60.0)	39	21 (53.8)	0.234	0.628
		Others	26	17 (65.4)	11	6 (54.5)	0.063 ^a	0.802 ^a
	Delayed (24-120 h)	Gastrointestinal	25	9 (36.0)	39	11 (28.2)	0.431	0.512
		Others	26	7 (26.9)	11	4 (36.4)	0.033 ^a	0.857 ^a
	Overall (0-120 h)	Gastrointestinal	25	9 (36.0)	39	11 (28.2)	0.431	0.512
		Others	26	6 (23.1)	11	3 (27.3)	0.022 ^a	0.883 ^a

The patients in the NK-1 RA group received NK-1 RA + tropisetron and those in the dexamethasone group received tropisetron + dexamethasone. ^a: Continuity correction χ^2 test. CR: Complete response; CC: Complete control; TR: Total response; NK-1: Neurokinin-1; RA: Receptor antagonist.

表 5 两组患者各疗效观察期治疗结果按肿瘤类型分层后的 CMH 检验结果

Tab 5 CMH test results of outcomes at different curative observation phases between 2 groups after stratification by tumor types

Outcome	Phase	Tumor type	OR (95% CI)		Homogeneity test of OR			
			Stratification	Total	OR (95% CI)	<i>P</i> value		
CR of vomiting	Acute (0-<24 h)	Gastrointestinal	0.738 (0.197, 2.768)	0.865 (0.330, 2.263)	0.762 (0.275, 2.114)	0.601		
		Others	0.800 (0.160, 4.003)					
	Delayed (24-120 h)	Gastrointestinal	0.454 (0.155, 1.381)	0.820 (0.369, 1.822)			0.789 (0.342, 1.820)	0.579
		Others	2.286 (0.493, 10.605)					
	Overall (0-120 h)	Gastrointestinal	0.656 (0.234, 1.840)	0.891 (0.405, 1.961)			0.789 (0.342, 1.820)	0.579
		Others	1.500 (0.352, 6.397)					
CC of nausea	Acute (0-<24 h)	Gastrointestinal	0.632 (0.203, 1.963)	0.673 (0.289, 1.564)	0.594 (0.243, 1.453)	0.253		
		Others	0.533 (0.125, 2.273)					
	Delayed (24-120 h)	Gastrointestinal	0.373 (0.133, 1.049)	0.753 (0.343, 1.652)			0.751 (0.338, 1.671)	0.483
		Others	2.800 (0.650, 12.064)					
	Overall (0-120 h)	Gastrointestinal	0.458 (0.164, 1.282)	0.653 (0.294, 1.453)			0.578 (0.250, 1.338)	0.200
		Others	0.914 (0.212, 3.939)					
TR of nausea and vomiting	Acute (0-<24 h)	Gastrointestinal	0.778 (0.275, 2.114)	0.697 (0.315, 1.543)	0.728 (0.317, 1.670)	0.453		
		Others	0.635 (0.275, 2.114)					
	Delayed (24-120 h)	Gastrointestinal	0.698 (0.239, 2.044)	0.938 (0.402, 2.185)			0.913 (0.381, 2.188)	0.838
		Others	1.551 (0.345, 6.975)					
	Overall (0-120 h)	Gastrointestinal	0.698 (0.239, 2.044)	0.933 (0.394, 2.211)			0.835 (0.341, 2.047)	0.694
		Others	1.250 (0.250, 6.255)					

CMH: Cochran-Mantel-Haenszel; CR: Complete response; CC: Complete control; TR: Total response; OR: Odds ratio; CI: Confidence interval.

2.4 两组止吐方案的安全性分析 两组患者在治疗过程中均出现不同程度的不良反应(表6)。与止吐药物相关的不良反应症状主要为乏力、便秘、呃逆、失眠,症状分级大多为1~2级。NK-1 RA组便秘的发生率(31.4%, 16/51)略高于地塞

米松组(26.0%, 13/50),乏力、呃逆、失眠的发生率略低于地塞米松组,两组间上述症状发生率差异均无统计学意义(均 $P>0.05$)。两组间各实验室指标异常的发生率差异也均无统计学意义(均 $P>0.05$)。

表6 两组患者不良反应发生率的比较

Tab 6 Comparison of incidence of adverse events between 2 groups

Adverse event	NK-1 RA group <i>N</i> =51			Dexamethasone group <i>N</i> =50			Z value	<i>P</i> value
	No	Grade 1-2	Grade 3-4	No	Grade 1-2	Grade 3-4		
Symptom								<i>n</i> (%)
Weak	38 (74.5)	10 (19.6)	3 (5.9)	38 (76.0)	12 (24.0)	0	-0.335	0.738
Constipation	35 (68.6)	15 (29.4)	1 (2.0)	37 (74.0)	13 (26.0)	0	-0.649	0.516
Hiccough	42 (82.4)	9 (17.6)	0	34 (68.0)	15 (30.0)	1 (2.0)	-1.701	0.089
Insomnia	39 (76.5)	12 (23.5)	0	35 (70.0)	15 (30.0)	0	-0.946	0.344
Laboratory indicator abnormality								
Leukocyte decrease	43 (84.3)	6 (11.8)	2 (3.9)	45 (90.0)	5 (10.0)	0	0.081	0.516
Neutrophil decrease	47 (92.2)	3 (5.9)	1 (2.0)	46 (92.0)	4 (8.0)	0	-0.176	0.675
Hemoglobin decrease	48 (94.1)	2 (3.9)	1 (2.0)	47 (94.0)	2 (4.0)	1 (2.0)	0.088	0.684
Platelet decrease	45 (88.2)	5 (9.8)	1 (2.0)	44 (88.0)	5 (10.0)	1 (2.0)	-0.001	0.874
ALT and/or AST increase	47 (92.2)	4 (7.8)	0	44 (88.0)	5 (10.0)	1 (2.0)	0.145	0.704
Serum creatinine increase	47 (92.2)	4 (7.8)	0	48 (96.0)	2 (4.0)	0	0.133	0.515

The patients in the NK-1 RA group received NK-1 RA+tropisetron and those in the dexamethasone group received tropisetron+dexamethasone. NK-1: Neurokinin-1; RA: Receptor antagonist; ALT: Alanine transaminase; AST: Aspartate transaminase.

3 讨论

本研究是针对接受MEC的患者设计的前瞻性随机对照试验,旨在探讨MEC治疗中NK-1 RA(阿瑞匹坦或福沙匹坦)联合托烷司琼的二联止吐方案疗效是否不劣于地塞米松联合托烷司琼的标准一线二联止吐方案,为探索去糖皮质激素化MEC止吐方案的可行性提供依据。

有多项临床研究探讨了减少地塞米松使用天数对CINV治疗效果的影响。Ito等^[7]采用NK-1 RA、帕洛诺司琼联合地塞米松三联方案预防HEC-CINV,比较了地塞米松1d用药方案与地塞米松连续3d用药方案的疗效,发现两组总观察期的CR率相似。Aapro等^[8]采用帕洛诺司琼联合地塞米松方案预防MEC-CINV,对比了地塞米松仅在第1天使用(第2~3天使用安慰剂)与第1~3天连续使用的疗效,结果显示在总观察期单日使用地塞米松组CR率不劣于3日组。但这些方案仍未完全停用地塞米松。针对这一争议,有学者开始设计并在ClinicalTrials.gov和ChiCTR注册头对头临床研究,探索非地塞米松CINV止吐方案的可行性。

本研究结果显示,去地塞米松的NK-1 RA(阿

瑞匹坦或福沙匹坦)联合5-HT₃ RA对MEC-CINV控制良好,且在急性期及延迟期其疗效不劣于指南推荐的托烷司琼+地塞米松标准二联止吐方案。此研究结论与2022年公布的一项III期临床研究结果^[9]类似。该研究在接受mFOLFOX6(奥沙利铂、亚叶酸钙和5-氟尿嘧啶)MEC方案的患者中观察了2种方案对CINV的预防效果,结果显示总观察期和延迟期阿瑞匹坦联合帕洛诺司琼组CR率高于地塞米松联合帕洛诺司琼组(88.8% vs 74.2%, $P=0.001$; 90.6% vs 75.5%, $P<0.0001$),急性期两组的CR率均 $>90%$ 且差异无统计学意义($P=0.94$)。在恶心症状控制方面,本研究结果显示NK-1 RA联合托烷司琼的表现也不劣于地塞米松联合托烷司琼(各疗效观察期 $P_{非劣效}<0.025$),但也未体现显著的优势。这与既往的研究结果^[10-11]一致,这2项研究在5-HT₃ RA联合地塞米松方案中加入阿瑞匹坦预防MEC-CINV,虽然总体CR率提高,但未能使恶心症状得到明显缓解。

在本研究中,对于呕吐的控制,两组各疗效观察期的CR率都明显低于现有研究结果。如Weinstein等^[12]的研究发现采用联合止吐治疗后,急性期CR率为91.0%,延迟期和总观察期的CR

率分别为 68.5% 和 66.9%。分析原因可能与本研究选择了第 1 代 5-HT₃ RA 托烷司琼有关,有研究显示第 2 代 5-HT₃ RA 的疗效显著优于第 1 代 5-HT₃ RA^[13]。同时本研究未对患者基线特征设置严格限制,未统一患者的化疗方案,这可能也会导致研究结果的差异。

此外,本研究观察到两组间不良反应发生率差异无统计学意义,两组不良反应发生率均未超过本试验的预期估计值,这表明患者对 NK-1 RA 联合托烷司琼止吐方案的耐受性良好,其不良反应的发生率与标准阳性对照组无显著差别。

综上所述,本研究结果提示对于接受 MEC 的患者,NK-1 RA 联合托烷司琼的二联止吐方案对 CINV 的预防效果不劣于含地塞米松的标准二联止吐方案,且安全性良好,但本研究对入组患者未做严格基线限制,如是否首次化疗、肿瘤类型、化疗方案等,虽然使用分层分析验证了两组间肿瘤类型的差异不影响研究结论的可靠性,仍然不能忽视这些混杂因素对研究结果的影响。此外,本研究纳入的样本量较小,需在今后的研究中优化研究设计及扩大样本量。

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