三磷酸腺苷结合盒转运体C2基因遗传变异与TA方案新辅助化疗乳腺癌患者骨髓抑制的关联研究

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摘　要:[目的]探讨三磷酸腺苷结合盒转运体C2(ATP binding cassette subfamily C member 2,ABCC2)基因单核苷酸多态性(single nucleotide polymorphism,SNP)与TA方案(紫衫类药物+蒽环类药物)新辅助化疗乳腺癌患者骨髓抑制的相关性。[方法]556例采用TA方案新辅助化疗的女性乳腺癌患者,化疗前抽取2ml静脉血,筛选标签SNP,采用Sequenom MassARRAY基因分型平台进行标签SNP分型,并分析标签SNP与乳腺癌患者骨髓抑制的关系。采用多因素Logistic回归分析计算风险比及其95%可信区间。[结果]筛选出3个标签SNP rs717620、rs3740066、rs2273697。与携带rs717620CC基因型相比,携带rs717620 CT基因型患者骨髓抑制程度更重,OR及其95%CI为1.72(1.18~2.52)。与携带rs3740066 CC基因型相比,携带rs3740066 CT基因型患者骨髓抑制程度更重,OR及其95%CI为1.47(1.02~2.12)。累积分析显示,随着风险基因型个数的增加,乳腺癌新辅助化疗患者的骨髓抑制风险增加,OR及其95%CI为1.27(1.05~1.53);与0个风险基因型相比,携带2个风险基因型患者骨髓抑制程度更重,OR及其95%CI为1.30(1.07~1.57)。[结论]ABCC2基因rs717620和rs3740066与TA方案新辅助化疗乳腺癌患者的骨髓抑制相关,可作为预测乳腺癌新辅助化疗患者骨髓抑制的生物标志物。
关键词:乳腺肿瘤;三磷酸腺苷结合盒转运体C2基因;多态性,单核苷酸;新辅助化疗;骨髓抑制
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Association of ABCC2 Gene Polymorphism with Myelosuppression in Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy of TA Regimen

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Abstract:[Purpose] To assess the association of single nucleotide polymorphisms (SNPs) in ABCC2(ATP binding cassette subfamily C member 2) gene with myelosuppression of breast cancer(BC) patients undergoing neoadjuvant chemotherapy of TA (taxane and antharcycline) regimen. [Methods] Total 556 female BC patients were recruited and treated with neoadjuvant chemotherapy of TA regimen. Blood samples were collected from patients before chemotherapy. Tagging SNPs(tag-SNPs) were selected,and the association of tag-SNPs with myelosuppression was analyzed by Sequenom Mass ARRAY system platform. The odds ratios (ORs) and 95% confidence intervals (CIs) for myelosuppression were calculated by multivariate logistic regression model. [Results] Three tag-SNPs(rs717620,rs3740066,rs2273697) were selected for study. Compared with individuals carrying rs717620 CC genotype,the risk of myelosuppression was significantly increased in individuals carrying rs717620 CT genotype (OR=1.72,95%CI:1.18~2.52,P<0.005). Compared with individuals carrying the rs3740066 CC genotype,the risk of myelosuppression was significantly increased in individuals carrying rs3740066 CT genotype had worse myelosuppression(OR=1.47,95%CI:1.02~2.12,P<0.038). Accumulation analysis showed that with the increase of the number of risk genotypes,the risk of myelosuppression increased (OR=1.27,95%CI:1.05~1.53,P<0.013). Compared with individuals carrying no risk genotype,individuals carrying two risk genotypes had worse myelosuppression (OR=1.30,95% CI:1.07~1.57,P<0.008). [Conclusion] The variations of rs717620 and rs3740066 in ABCC2 gene are significantly associated with myelosuppression,which might serve as biomarkers for predicting myelosuppression in BC patients treated with neoadjuvant chemotherapy of TA regimen.
Key words:breast neoplasms;ABCC2 gene;polymorphism,single nucleotide;neoadjuvant chemotherapy;myelosuppression

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化疗引起的严重白细胞减少常导致停药或治疗延迟、剂量不足，甚至导致化疗终止，最终可能危及长期临床疗效，缩短无病生存期和总生存期[1-2]。严重的骨髓抑制是乳腺癌治疗失败的重要原因，而较好的化疗疗效和较轻的骨髓抑制更利于患者生存以及获得更好的生活质量。因此，在TA方案化疗过程中，明确TA诱导的骨髓抑制的影响因素，以监测骨髓抑制，确保TA方案具有更高的疗效或更低的血液毒性显得尤为重要。

对于治疗窗较窄的药物而言，临床药物反应的个体差异是产生药物毒性的一个决定因素。药物遗传学研究表明，药物相关基因调控区遗传变异，如单核苷酸多态性(single nucleotide polymorphism，SNP)可显著影响基因表达，而编码区的遗传变异主要影响所编码蛋白的氨基酸组成，从而导致该蛋白的一级结构和生物活性改变[3-4]，使肿瘤细胞对化疗药物产生耐受。基因多态性是引起个体差异的主要原因之一，通常改变药物的药动学参数，继而影响药物疗效或药物不良反应[5]。也有研究显示，SNP可能是影响乳腺癌化疗骨髓抑制的重要因素[6]。

三磷酸腺苷结合盒转运体C2(ATP binding cassette subfamily C member 2，ABCC2)，又称为多药耐药蛋白2，是由ABCC2基因编码的一种有机阴离子转运蛋白，能够运输阴离子药物和酸性配体结合的中性药物。多项研究表明，蒽环类药物或紫杉类药物是多药耐药蛋白2的转运底物之一[7]，并且ABCC2还与蒽环类和紫杉类药物的耐药性有关[7-8]。ABCC2可能是一种高亲脂性抗癌药物的药代动力学行为的主要决定因素，已被证明其在小鼠模型的体内紫杉醇药代动力学中发挥重要作用[9]。ABCC2基因SNP可能通过改变转运蛋白基因的表达水平或结构，导致其转运功能发生改变[10]，从而影响体内蒽环类药物或紫杉类药物的浓度。由此可见，ABCC2基因的遗传变异可能是影响乳腺癌化疗骨髓抑制的重要因素。本研究中，我们分析了ABCC2基因SNP与TA方案新辅助化疗乳腺癌患者骨髓抑制的相关性，以探讨ABCC2基因SNP在预测乳腺癌患者新辅助化疗骨髓抑制中的价值。

1 材料与方法

1.1 研究对象

入组标准：①病理诊断为浸润性乳腺癌；②根据美国癌症联合委员会(American Joint Committee on cancer，AJCC)乳腺癌TNM分期标准(第6版)，临床分期为Ⅱ~Ⅲ期；③无其他原发肿瘤；④来自中国汉族人群，患者之间无直系亲属关系；⑤初诊患者，在中国医学科学院肿瘤医院接受TA方案新辅助化疗，化疗之前未接受任何乳腺癌相关治疗。

2003年1月至2016年12月符合入组条件的乳腺癌患者556例，均为女性，年龄23~72岁，中位年龄为48岁。

1.2 资料收集

通过病历收集年龄、性别、绝经状态、雌激素受体(estrogen receptor，ER)状态、孕激素受体(progesterone receptor，PR)状态、人表皮生长因子受体-2(human epidermal growth factor receptor-2，Her-2)状态、骨髓抑制、化疗周期以及剂量等信息。骨髓抑制评价依据美国国家癌症研究所制定的常规毒性标准3.0版(NCI-CTC 3.0)，骨髓抑制三、四级为重度骨髓抑制，其他等级为轻度骨髓抑制。本研究获得中国医学科学院肿瘤研究所和肿瘤医院伦理委员会的支持，患者均签署知情同意书。

1.3 治疗方法

患者均采用TA方案化疗。紫杉醇平均剂量为166.4mg/m^2，静脉滴注>3h；多西他赛平均剂量为70.2mg/m^2，静脉滴注>1h；表柔比星平均剂量为72.9mg/m^2，多柔比星的平均剂量为45.1mg/m^2，静脉滴注。每3周为1个周期，患者接受4~6个周期化疗，化疗后行手术治疗。

1.4 DNA提取和标签SNP分型

所有患者在化疗前抽取2ml外周静脉血，采用酚-氯仿法提取基因组DNA。根据国际千人基因组计划汉族人群基因型数据库(2013年6月公布的数据)，筛选位于ABCC2基因(基因长度71.14kb)以及基因上游2kb范围内中国北京地区汉族人群次要等位基因频率≥0.10的所有功能区域SNP，进行连锁不平衡分析，样本量大小的膨胀因子r^2>0.8。根据HapMap计划发布的中国北京地区汉族人群基因型数据库(Rel 27 Phase Ⅱ+Ⅲ Feb09，NCBI B36 assembly，dbSNP b126)采用单体型域的方法挑选标签SNP，样本量大小的膨胀因子r^2>0.8[11]。采用Sequenom MassARRAY基因分型平台进行标签SNP分型。SNP分型质量控制：每板(96个检测样本)中有1个阴性对照、1个阳性对照、2个重复随机样本对照(重复样

本符合率 100%)。

1.5 统计学方法

用 SPSS 18.0 统计分析。χ^2 检验分析标签 SNP 的 Hardy-Weinberg 平衡 (Hardy-Weinberg equilibrium, HWE)。多因素 Logistic 回归模型计算乳腺癌 TA 方案新辅助化疗乳腺癌患者骨髓抑制的风险比(odds ratio,OR) 及其 95%可信区间 (confidence interval, CI)。Haploview 软件 (v4.4) 分析同一条染色体上 SNP 之间的连锁不平衡。所有的检验均为双侧检验,检验水准 α=0.05。

2 结 果

2.1 研究对象的临床基本资料

556 例患者中,重度骨髓抑制患者 331 例(59.5%),轻度骨髓抑制患者 225 例(40.5%)。绝经后患者 231 例,ER、PR 和 Her2 均阴性 390 例,Ⅱ期、Ⅲ期分别为 237 例、319 例。3~4 个周期化疗患者 405 例(72.0%)(Table 1)。单因素 Logistic 回归分析显示,48 岁以上的患者骨髓抑制更严重,OR 为 1.55,95%CI 为 1.10~2.19,不同骨髓抑制状态的患者紫杉醇、多西他赛、表柔比星、多柔比星的总剂量强度差异无统计学意义。多因素 Logistic 回归分析,不同年龄层患者的骨髓抑制差异无统计学意义(Table 2)。

2.2 TA 方案新辅助化疗乳腺癌患者骨髓抑制相关的 ABCC2 基因多态

筛选出 3 个标签 SNP,分别是 rs717620、rs3740066 和 rs2273697,均符合 Hardy-Weiberg 平衡定律 (P 值分别为 0.826、0.275 和 0.395)。rs717620 和 rs3740066 与 TA 方案新辅助化疗乳腺癌患者骨髓抑制显著相关,但 rs2273697 与 TA 方案新辅助化疗乳腺癌患者骨髓抑制无显著相关性。

携带 rs717620 CC、CT、TT 基因型患者重度骨髓抑制比例分别为 59.2%、36.9%、3.9%。与携带 rs717620 CC 基因型相比,携带 rs717620 CT 基因型患者骨髓抑制程度更重,OR 及其 95%CI 为 1.72 (1.18~2.52)。显性模型:多因素 Logistic 回归分析结果显示,携带 T 等位基因患者的骨髓抑制程度更重,OR 及其 95%CI 为 1.64(1.14~2.36)。累加模型:多因素 Logistic 回归分析结果显示,乳腺癌新辅助化疗患者的骨髓抑制 OR 及其 95%CI 为 1.43(1.04~1.95)(Table 3)。

携带 rs3740066 CC、CT、TT 基因型患者重度骨髓抑制比例分别为 56.6%、39.1%、4.3%。与携带 rs3740066 CC 基因型相比,携带 rs3740066 CT 基因型患者骨髓抑制程度更重,OR 及其 95%CI 为 1.47 (1.02~2.12)。显性模型:多因素 Logistic 回归分析结果显示,携带 T 等位基因患者的骨髓抑制程度更重,OR 及其 95%CI 为 1.46(1.03~2.08)(Table 3)。

Table 1 Clinical characteristics of myelosuppression in breast cancer patients treated with neoadjuvant chemotherapy of TA regimen

Characteristics	Number of patients (%)	Myelosuppression [a]	
		Severe (%)	General (%)
Age (years)			
≤48	290(52.2)	158(47.7)	132(58.7)
>48	266(47.8)	173(52.3)	93(41.3)
Menopausal status			
No	325(58.5)	185(55.9)	140(62.2)
Yes	231(41.5)	146(44.1)	85(37.8)
ER status			
Negative	216(38.8)	130(39.3)	86(38.2)
Positive	340(61.2)	201(60.7)	139(61.8)
PR status			
Negative	240(43.2)	137(41.4)	103(45.8)
Positive	316(56.8)	194(58.6)	122(54.2)
HER-2 status			
Negative	334(60.1)	193(58.3)	141(62.7)
Positive	134(24.1)	82(24.8)	52(23.1)
Unknown	88(15.8)	56(16.9)	32(14.2)
ER/ PR/HER-2 status			
Negative	390(70.1)	234(70.7)	156(69.3)
Positive	78(14.1)	41(12.4)	37(16.5)
Unknown	88(15.8)	56(16.9)	32(14.2)
TNM stage			
Ⅱ	237(42.6)	131(39.6)	106(47.1)
Ⅲ	319(57.4)	200(60.4)	119(52.9)
Cycles of chemotherapy(cycles)			
3~4	405(72.8)	242(73.1)	163(72.4)
5~6	151(27.2)	89(26.9)	62(27.6)
Total dose intensity(Mean±SE)(mg/m^2)			
Taxane-based			
Paclitaxel	461(82.9)	732.0±9.9	723.7±12.2
Docetaxel	95(17.1)	318.3±10.5	319.5±11.7
Antharcycline-based			
Epirubicin	495(89.0)	324.2±4.5	321.7±5.5
Doxorubicin	61(11.0)	194.1±9.2	182.6±13.5

Notes:OR:odds ratio;CI:confidence interval;ER:estrogen receptor;PR:progesterone receptor;HER-2:human epidermal growth factor receptor-2. [a]:general,0-2 grade;severe 3-4 grade,according to NCI-CTC 3.0

Table 2 Association of clinical characteristics with myelosuppression in breast cancer patients treated with neoadjuvant chemotherapy of TA regimen

Characteristics	OR (95%CI)	*P*	OR [a] (95% CI)	*P*[a]
Age(years)				
≤48	1.00(reference)		1.00(reference)	
>48	1.55(1.10~2.19)	0.011	1.59(0.92~2.74)	0.098
Menopausal status				
No	1.00(reference)		1.00(reference)	
Yes	1.30(0.92~1.84)	0.137	0.93(0.53~1.63)	0.808
ER status				
Negative	1.00(reference)		1.00(reference)	
Positive	0.96(0.68~1.36)	0.803	0.81(0.49~1.33)	0.405
PR status				
Negative	1.00(reference)		1.00(reference)	
Positive	1.20(0.85~1.68)	0.305	1.44(0.90~2.30)	0.134
HER-2 status				
Negative	1.00(reference)		1.00(reference)	
Positive	1.15(0.77~1.74)	0.498	1.16(0.74~1.80)	0.517
ER/ PR/HER-2 status				
Negative	1.00(reference)		1.00(reference)	
Positive	0.74(0.45~1.20)	0.224	0.74(0.45~1.21)	0.230
TNM stage				
Ⅱ	1.00(reference)		1.00(reference)	
Ⅲ	1.04(0.74~1.46)	0.830	0.87(0.57~1.33)	0.524
Cycles of chemotherapy(cycles)				
3~4	1.00(reference)		1.00(reference)	
5~6	0.97(0.66~1.41)	0.862	1.03(0.70~1.51)	0.901
Total dose intensity				
Taxane-based				
Paclitaxel	NA	0.5958[b]	NA	NA
Docetaxel	NA	0.9397[b]	NA	NA
Antharcycline-based				
Epirubicin	NA	0.7267[b]	NA	NA
Doxorubicin	NA	0.4709[b]	NA	NA

Notes:OR:odds ratio;CI:confidence interval;NA:not applicable;ER:estrogen receptor;PR:progesterone receptor;HER-2:human epidermal growth factor receptor-2; [a]:adjusting for age,menopausal status,ER status,PR status,HER-2 status,TNM stage and cycles of chemotherapy; [b]:Two-sided *t* test

2.3 累积风险基因型与 TA 方案新辅助化疗患者骨髓抑制的关联分析

根据患者骨髓抑制程度与 ABCC2 基因 SNP 关联分析的结果，将 rs717620 CT、rs717620 TT、rs3740066 CT 和 rs3740066 TT 作为风险基因型。

携带 0 个风险基因型、1 个风险基因型、2 个风险基因型患者重度骨髓抑制比例分别为 55.0%、5.5%和 39.5%，轻度骨髓抑制比例分别为 62.1%、10.7%和 27.2%。与 0 个风险基因型相比，携带 2 个风险基因型患者骨髓抑制程度更重，OR 及其 95%CI 为 1.30(1.07~1.57)。累加模型：多因素 Logistic 回归分析结果显示，随着风险基因型个数的增加，乳腺癌新辅助化疗患者的骨髓抑制风险增加，OR 及其 95%CI 为 1.27(1.05~1.53)(Table 4)。

3 讨 论

本研究中我们发现的与 TA 方案新辅助化疗乳腺癌患者骨髓抑制相关的 SNP 位点 rs717620、rs3740066 分别位于 ABCC2 基因编码的 5′非转录区域和外显子区。ABCC2 基因位于人类基因组 10q24.2 区域，编码的多药耐药相关蛋白 (multidrug resistance-associated protein 2,MRP2)主要分布于肝细胞的管腔膜、肾近端小管细胞的管腔膜侧[12]，以及多种人类肿瘤细胞[13]，且 MRP2 在肿瘤细胞中的表达差异可影响肿瘤细胞对化疗药物的耐药性[14]。位于细胞膜上 MRP2 将药物从细胞内泵出细胞以降低细胞内药物浓度和减轻细胞毒性作用，进而使耐药性增强。稳定表达人 ABCC2 的 HEK-293 细胞对阿霉素和表阿霉素的抗药性升高相关[15]。在卵巢癌中，ABCC2 基因高表达增强了细胞对顺铂的耐药性，但 ABCC2 基因外显子上的 SNP 发生氨基酸替换，降低了细胞的顺铂耐药性[16-17]，此外，氨基葡萄糖可逆转 MRP2 过表达卵巢癌细胞的药物耐药性[18]。可见 ABCC2 基因遗传变异以及 MRP2 在肿瘤细胞药物耐药性中发挥重要作用[10]。

ABCC2 基因 rs717620 位于 5′非转录区域区，此突变可能与 MRP2 的表达水平和活性相关。有研究发现 rs717620 的变异与白种人 mRNA 低表达和抗癫痫药物耐药有关[19]，但在亚洲人群不相关。一项系统荟萃分析显示，rs717620 是癫痫患者抗癫痫药物较差疗效的重要预测因子，但在亚洲人口中并未发现该相关性[20]。Haenisch 等[21]研究发现，rs717620 核苷酸改变与 ABCC2 基因 mRNA 和 MRP2 蛋白表达的减少、蛋白活性减小相关。Razali 等[22]研究发现，

Table 3 Association of rs717620 and rs3740066 with myelosuppression in breast cancer patients treated with neoadjuvant chemotherapy of TA regimen

Genotypes	Myelosuppression		OR[a](95%CI)	P [a]
	Severe(%)	General(%)		
rs717620[b]				
CC	196(59.2)	157(70.1)	1.00(reference)	
CT	122(36.9)	58(25.9)	1.72(1.18~2.52)	0.005
TT	13(3.9)	9(4.0)	1.06(0.68~1.65)	0.796
Dominant mode			1.64(1.14~2.36)	0.008
Recessive mode			1.06(0.44~2.53)	0.903
Additive mode			1.43(1.04~1.95)	0.026
rs3740066 [c]				
CC	185(56.6)	146(64.9)	1.00(reference)	
CT	128(39.1)	71(31.6)	1.47(1.02~2.12)	0.038
TT	14(4.3)	8(3.5)	1.16(0.74~1.83)	0.512
Dominant mode			1.46(1.03~2.08)	0.036
Recessive mode			0.85(0.35~2.07)	0.718
Additive mode			1.35(0.99~1.84)	0.055

Notes: OR: odds ratio; CI: confidence interval; [a]: adjusting for age; [b]: one sample genotyping failure; [c]: four samples genotyping failure

Table 4 Accumulation analysis of the association between risk genotypes of rs717620 and rs3740066 and myelosuppression in breast cancer patients treated with neoadjuvant chemotherapy of TA regimen

Risk genotypes [a]	Myelosuppression		OR [b] (95%CI)	P [b]
	Severe(%)	General(%)		
0	180(55.0)	139(62.1)	1.00(reference)	
1	18(5.5)	24(10.7)	0.58(0.30~1.12)	0.103
2	129(39.5)	61(27.2)	1.30(1.07~1.57)	0.008
Additive mode			1.27(1.05~1.53)	0.013

Notes: OR: odds ratio; CI: confidence interval; a: Five samples genotyping failure. Risk genotypes: rs717620 CT, rs717620 TT, rs3740066 CT, rs3740066 TT. The number of risk genotypes was the sum of meylosuppression risk genotypes in these two loci; b: adjusting for age

rs717620 与马来西亚儿童急性淋巴细胞白血病治疗后 48 小时血清甲氨蝶呤浓度水平和甲氨蝶呤的毒副作用显著相关。Liu 等[23]研究发现，在中国急性淋巴细胞白血病患儿中，rs717620 核苷酸改变显著增加了甲氨蝶呤首次给药 48h 后的血药浓度，同时也显著增加了甲氨蝶呤的毒副作用，包括血液系统毒性。另外在黎巴嫩急性淋巴细胞白血病患儿中，同样研究发现携带 ABCC2-24C>T 核苷酸改变的患儿血液中甲氨蝶呤的浓度明显增加，若持续给药，需要降低甲氨蝶呤的给药量，以降低毒副作用[24]。本研究与甲氨蝶呤药物引起的毒副作用一致，携带 rs717620 T 等位基因的患者的 TA 方案引起骨髓抑制显著增加，OR 及其 95%CI 为 1.64(1.14~2.36)。另外，还有研究发现 rs717620 与霉酚酸酯引起的胃肠道不良反应甚至被迫停药明显相关[25]，与双氯酚钠产生的肝脏毒性相关[26]。

rs3740066 位于 ABCC2 基因第 28 号外显子区，属于同义替换，可能改变了 ABCC2 mRNA 的二级结构造成 mRNA 稳定性的变化，影响蛋白质的表达水平。rs3740066 被报道与中国癫痫患者[27]和马来西亚的女性隐源性癫痫患者[28]对抗癫痫药物的耐药相关，但日本[29]和奥地利[30]的研究并未得出一致结果。荟萃分析还表明，rs3740066 与亚洲人群癫痫患者的药物反应无关[20]。Sharifi 等[31]研究结果显示甲氨蝶呤治疗的急性淋巴细胞白血病患儿的肝脏毒性与 rs3740066 显著相关。Sagi 等[32]研究发现 rs3740066 可能调节急性淋巴细胞白血病与骨肉瘤患者蒽环类药物化疗后心脏毒性的个体风险。本研究发现 rs3740066 与 TA 方案化疗骨髓抑制显著相关，携带 T 等位基因患者的骨髓抑制程度更重。

rs2273697 位于 ABCC2 基因第 11 号外显子区，此突变为错义突变，可引起 MRP2 中跨膜区域 V417I 氨基酸替换，可能会改变转运蛋白的转运活性，但是改变情况可能视底物药物和人群种族而异。有研究显示 rs2273697 与卡马西平引起的神经性不良反应显著相关[33]。但该结果在另外一篇文献中未得到一致结果，甚至认为卡马西平根本不是 MRP2 的底物[34]。最近发表的两篇荟萃分析认为 rs2273697 显著降低癫痫患者对抗癫痫药物的耐药风险[35-36]。但本研究并未发现 rs2273697 与乳腺癌患者 TA 方案化疗引起的骨髓抑制显著相关。

到目前为止，尚无文献报道 rs717620、rs3740066 与 TA 方案新辅助化疗乳腺癌患者骨髓抑制的关系。值得庆幸的是，我们的研究中首次发现 rs717620 和 rs3740066 与 TA 方案化疗引起的骨髓抑制有显著的相关性。这两个 SNP 或者与其强连锁不平衡的 SNP 可能会影响 ABCC2 基因的表达水平或改变 ABCC2 蛋白的功能，从而影响 TA 方案诱导的骨髓抑制风险。还需要进一步的研究来阐明 TA 方案化疗药物骨髓抑制的生物学机制。

综上所述，ABCC2 基因中 rs717620 和 rs3740066 与 TA 方案新辅助化疗乳腺癌患者的骨髓抑制有关。可作为预测乳腺癌患者新辅助化疗骨髓抑制程度的遗传标志。

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